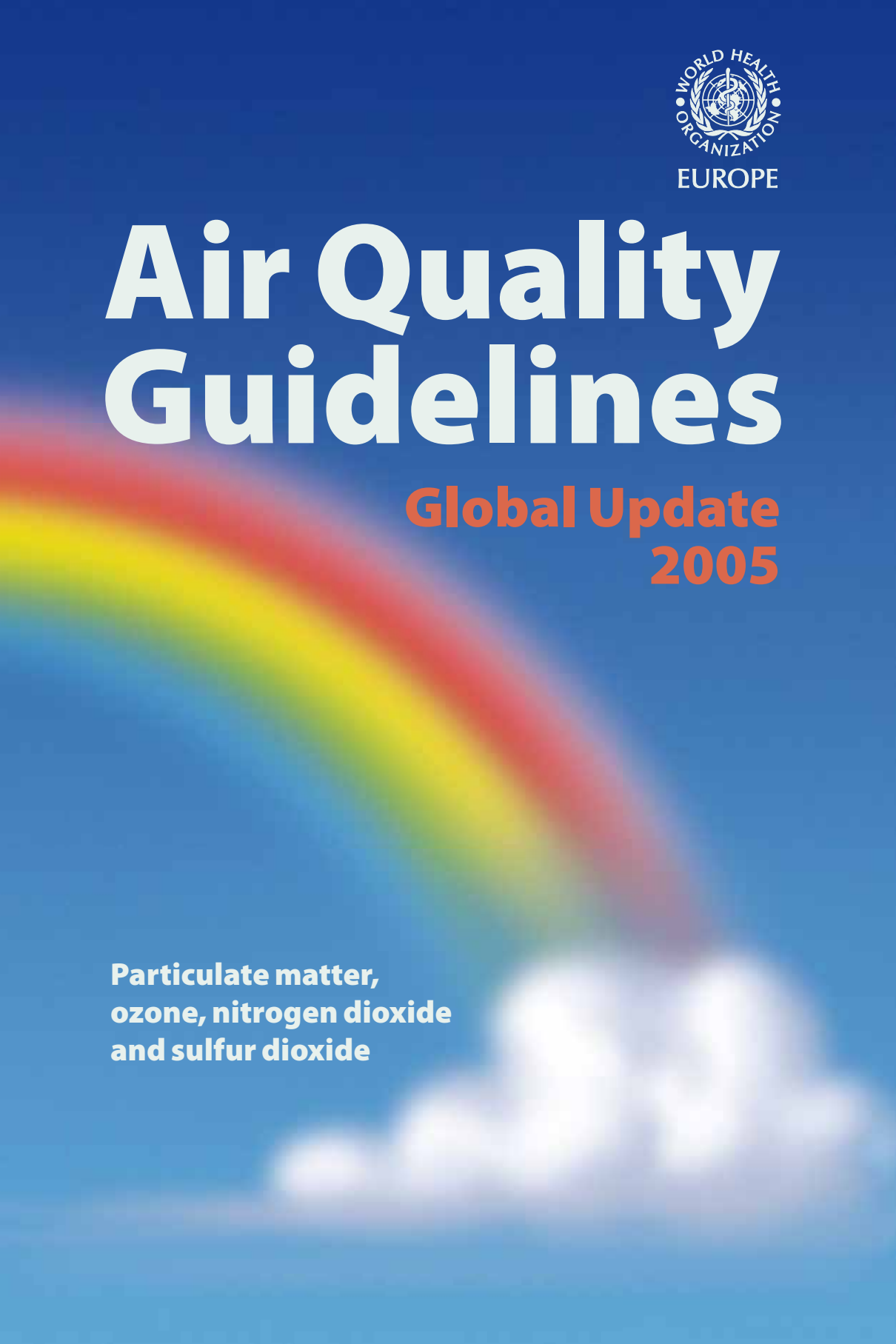
WORLD HEALTH ORGANIZATION
EUROPE
Air Quality Guidelines
Global Update 2005
Particulate matter, ozone, nitrogen dioxide and sulfur dioxide

Air Quality Guidelines
Global Update 2005

Abstract

The WHO air quality guidelines offer guidance to policy-makers on reducing the effects on health of air pollution. This book presents revised guideline values for the four most common air pollutants – particulate matter, ozone, nitrogen dioxide and sulfur dioxide. It also gives a comprehensive review of the issues affecting the use of the guidelines, which now apply the world over, in risk assessment and policy development.

Keywords
AIR - standards
AIR POLLUTION - analysis
AIR POLLUTANTS - adverse effects
AIR POLLUTION, INDOOR
OZONE - adverse effects
NITROGEN DIOXIDE - adverse effects
SULFUR DIOXIDE - adverse effects
ENVIRONMENTAL MONITORING
RISK ASSESSMENT
GUIDELINES

ISBN 92 890 2192 6

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Printed in Germany by Druckpartner Moser

EUROPE

Air Quality Guidelines

Global Update 2005

**Particulate matter,
ozone, nitrogen dioxide
and sulfur dioxide**

Acknowledgements

This work was supported by grants obtained by WHO from the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, the Energy Research Centre of the Netherlands, the Swiss Federal Office for the Environment, the Department of Health in the United Kingdom and the United States Environmental Protection Agency.

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Foreword

Clean air is a basic requirement of human health and well-being. Air pollution, however, continues to pose a significant threat to health worldwide. According to a WHO assessment of the burden of disease due to air pollution, more than two million premature deaths each year can be attributed to the effects of urban outdoor air pollution and indoor air pollution (from the burning of solid fuels). More than half of this disease burden is borne by the populations of developing countries. This update of the WHO air quality guidelines has been developed in response to this real and global threat to public health. It continues the long WHO tradition of supporting its Member States with the best available evidence on health determinants, and on the risks of air pollution in particular. Previous editions of the guidelines found wide application in environmental and public health decision-making in various parts of the world.

Although these guidelines are neither standards nor legally binding criteria, they are designed to offer guidance in reducing the health impacts of air pollution based on expert evaluation of current scientific evidence. They are intended to be relevant to the diverse conditions of all WHO's regions, and to support a broad range of policy options for air quality management. Knowledge about the hazardous properties of the pollutants and indication of the risk related to exposure, summarized by the guidelines, provide an essential scientific contribution to the development of strategies for air quality management. Authorities preparing national strategies, especially in those countries that lack the necessary scientific infrastructure and resources to conduct their own assessments in support of public policy, will find the guidelines an essential resource.

The synthesis of the research results that underlie the guidelines has been conducted by outstanding scientists and was subject to scrupulous peer review. We are grateful to these experts for their efforts and believe that this work will contribute to improving the health of people in all regions of the world.

Margaret Chan
WHO Director-General

Marc Danzon
WHO Regional Director for Europe

Introduction

The first edition of the WHO *Air quality guidelines for Europe* was published in 1987, since when scientific knowledge about the effects of exposure to air pollution and the magnitude of its public health impact has increased exponentially. The first edition summarized scientific knowledge on the health hazards related to the 28 most common air pollutants, providing a uniform basis for risk assessment for national authorities responsible for protecting populations from the adverse effects of air pollution. In the early 1990s, the growing body of knowledge allowed WHO to initiate a process for revising the guidelines, resulting in publication of the second edition in 2000 both in hard copy, summarizing risk characterization of 37 pollutants *(1)*, and in an extended electronic version containing the full background material of the review (www.euro.who.int/document/e71922.pdf).

Since the publication of the second edition there has been an increasing awareness among scientists and policy-makers of the global nature and magnitude of the public health problems posed by exposure to air pollution, based on hundreds of new studies published in the scientific literature. The project "Systematic review of health aspects of air pollution in Europe", carried out by the WHO Regional Office for Europe to support the development of the European Union's Clean Air for Europe (CAFE) programme in 2002–2004, concluded that this new evidence warranted revision of the air quality guidelines for particulate matter (PM), ozone and nitrogen dioxide *(2)*. Of particular importance in deciding that the guidelines should apply worldwide was the substantial and growing evidence of the health effects of air pollution in the low- and middle-income countries of Asia, where air pollution levels are the highest *(3)*. WHO's comparative risk assessment *(4–6)* quantified the burden of disease due to air pollution worldwide and, as noted above, found the largest burden in the developing countries of Asia.

Development of the update

WHO established a steering group to advise and lead the guideline development process.[1] The steering group agreed on the scope and methodology of the update, and identified experts to contribute to the review of the scientific literature.

The steering group recommended to WHO experts in epidemiology, toxicology, air quality exposure assessment, air quality management and public policy,

[1] Steering group members: H. R. Anderson (United Kingdom), B. Brunekreef (Netherlands), B. Chen (China), A. Cohen (United States), R. Maynard (United Kingdom), I. Romieu (Mexico), K. R. Smith (United States) and S. Wangwongwatana (Thailand).

who would draft the guideline document. After review and approval by the steering group, initial drafts were distributed for external review to a wide group of experts in all the relevant disciplines. WHO also sought the opinions of air quality managers and policy-makers concerning the rationale and format of the guidelines, seeking to improve their applicability in various parts of the world. An effort was made to ensure representation of a wide selection of Member States from all WHO regions.

WHO convened the Working Group on Air Quality Guidelines in Bonn, Germany, on 18–20 October 2005 to finalize the updated guidelines. The tasks of the meeting were to formulate guidelines for four specific pollutants (PM, ozone, nitrogen dioxide and sulfur dioxide) and to agree on a supporting text. The Working Group consisted of the authors of the draft chapters, the external reviewers of the drafts and members of the steering group (see Annex 2). Dr Robert Maynard chaired the meeting, and Dr Aaron Cohen acted as meeting Rapporteur. Comments on the drafts of the background material, received from the reviewers, were circulated to the steering group members, authors and all reviewers in advance of the meeting. Since not all reviewers participated in the meeting, a list of those who submitted written comments but who were not present at the meeting is also presented in Annex 2.

In a series of plenary discussions and drafting sessions, the Working Group reviewed the general approach to the formulation of the guidelines, discussed outstanding comments from the reviewers and agreed on the general content of the background material. The drafting groups discussed in detail the formulation of the updated guidelines and the text supporting them. Final decisions concerning the recommended guidelines were arrived at in plenary by consensus. Following the Working Group meeting, a report was prepared presenting recommendations for updated guidelines for PM, ozone, nitrogen dioxide and sulfur dioxide and summarizing the Working Group's discussions *(7)*. The Working Group's recommendations were reviewed and cleared by WHO and announced as updated air quality guidelines *(8)*. The comments from the review and from the Working Group meeting were considered in preparing the next drafts of the background material. The steering group supervised the finalization of the text and assisted WHO in its discussions with the main authors, in the scientific editing of the chapters and in ensuring that the final text was consistent with the Working Group's recommendations.

Scope of the update

These updated guidelines comprise 13 chapters. Chapters 1–9 consist of background material, providing a concise yet comprehensive review of the issues affecting the application of the WHO air quality guidelines in risk assessment and policy development.

- Chapters 1 and 2 address the sources and emissions of the main pollutants presented in the guidelines and discuss their ambient concentrations in various parts of the world. This review demonstrates wide diversity of air quality in the world, posing quite different challenges to air quality management. In many areas with high levels of pollution, it is caused by the use of obsolete technologies and lack of pollution control systems. Pollution reduction is technically feasible, but political or socioeconomic conditions and lack of organizational capacity may limit the effectiveness of air quality management. Poverty may be an obstacle in achieving improvements in air quality. In many developed countries, air quality has already improved in the last few decades, owing largely to air quality regulation. Further progress, necessary to reduce the adverse health impacts of pollution observed even at those low levels, requires the development and use of new technologies and, often, a change in population lifestyle and the introduction of new approaches to urban development.
- Chapters 3–5 present important concepts and methods concerning the quantification of human exposure to air pollution and the assessment of its effects on health. Factors that determine individual susceptibility to air pollution are also reviewed.
- Chapter 6 discusses the issue of environmental equity, and documents the unequal distribution of health risks due to air pollution both within and among nations.
- Chapter 7 discusses methods for quantifying the health burden of air pollution that trigger policy reactions, and may be used to analyse the cost–effectiveness of various policy options.
- Chapter 8 discusses the use of the guidelines in developing air quality standards and other policy tools.
- Chapter 9 focuses on indoor air pollution, especially on the conditions prevalent in developing countries owing to the indoor combustion of solid fuels. Owing to the magnitude of the health impacts of this pollution and the need to use risk reduction approaches that possibly differ from those developed for urban air quality management, this chapter makes preliminary recommendations for future WHO work on this specific problem.
- Chapters 10–13 comprise reviews of the health effects of PM, ozone, nitrogen dioxide and sulfur dioxide, respectively. Health-based guidelines are presented for each pollutant, based on those reviews, together with the rationale for the decision to revise the guideline value or to retain the existing value. As noted above, the epidemiological evidence indicates that the possibility of adverse health effects remains even if the guideline value is achieved. For this reason, some countries might decide to adopt lower concentrations than the WHO guideline values as national air quality standards.

In addition to guideline values, interim targets are given for levels of PM, ozone and sulfur dioxide. These are proposed as incremental steps in a progressive reduction of air pollution, and are intended for use in areas where pollution is high. These targets aim to promote a shift from high air pollutant concentrations, with acute and serious health consequences, to lower concentrations. If these targets were to be achieved, one could expect significant reductions in risks for acute and chronic health effects from air pollution. Progress towards the guideline values should, however, be the ultimate objective of air quality management and health risk reduction in all areas.

The fact that other pollutants, such as carbon monoxide, were not included in the present review reflects the limited resources available to the project. As a result, the 2000 WHO guidelines *(1)* for pollutants not considered in the current update remain in effect. The steering group recommends that the update of the guidelines be expanded to include additional pollutants as soon as possible, as resources become available.

Key scientific issues in the development of the guidelines

The guidelines are based on the extensive scientific evidence on air pollution and its health consequences. Although this information has gaps and uncertainties, it offers a strong foundation for the guidelines. Several overall research findings need to be emphasized with regard to the guidelines.

First, the evidence for ozone and PM shows risks to health at concentrations currently found in many cities in developed countries; these epidemiological findings imply that guidelines cannot provide full protection, since thresholds below which adverse effects do not occur have not been identified.

Second, an increasing range of adverse health effects has been linked to air pollution, and at ever-lower pollutant concentrations. This is especially true of airborne PM. New studies use more refined methods and more subtle but sensitive indicators of effects such as physiological measures (e.g. changes in lung function, inflammation markers). Therefore, the updated guidelines could be based both on these sensitive indicators and on the most critical and traditional population health indicators, such as mortality and unscheduled hospital admissions.

Third, the complexity of the air pollution mixture has been better characterized, making more clear the limitations of controlling air pollution through guidelines for single pollutants. Nitrogen dioxide, for example, is a product of combustion and is generally found in the atmosphere in close association with other primary pollutants, including ultrafine particles. It is also a precursor of ozone and therefore co-exists in photochemically generated oxidant pollution. Nitrogen dioxide is itself toxic, and its concentrations are often strongly correlated with those of other toxic pollutants. As it is easier to measure, it is often used as a surrogate for the mixture as a whole. Achieving the guidelines for individual

pollutants such as nitrogen dioxide may therefore bring benefits for public health that exceed those anticipated based on estimates of the pollutant's specific toxicity.

The updated guidelines provide new values for three of the four pollutants examined. For two of them (PM and ozone), it is possible to derive a quantitative relationship between the concentration of the pollutant as monitored in ambient air and specific health outcomes (usually mortality). These relationships are invaluable for health impact assessment and allow insights into the mortality and morbidity burdens from current levels of air pollution, as well as the improvements in health that could be expected under different air pollution reduction scenarios. The estimates of disease burden can also be used for the purpose of estimating the costs and benefits of interventions that reduce air pollution.

It is worth noting that the second edition of the WHO guidelines *(1)* did not set a guideline value for PM, and instead offered guidance for risk managers in the form of a statistical model relating exposure to risk, suggesting that they quantify the risk at locally relevant exposure levels and use those local estimates to guide policy-making. This approach to no-threshold pollutants has been applied widely in risk management of environmental chemicals (e.g. in risk assessment of genotoxic carcinogens). Although WHO has not evaluated formally how this guidance has been used in air quality management, it was the view of Working Group members from developing countries that the approach taken for PM in the 2000 guidelines had not been well-accepted by air quality managers and policy-makers. Therefore the updated guidelines define concentrations for the considered pollutants, which, if achieved, would be expected to result in significantly reduced rates of adverse health effects. These concentrations should be based on the available scientific evidence and would provide an explicit objective for air quality managers and policy-makers to consider when setting national air quality standards and management strategies. Given that air pollution levels in some countries often far exceed the recommended guideline levels, interim target levels are proposed, in excess of the guideline levels themselves, to promote steady progress towards meeting the WHO guidelines.

The updated guidelines and air quality management

The guidelines are written for worldwide use, and are intended to support actions aiming for the optimal achievable level of air quality in order to protect public health in different contexts. Air quality standards are an important instrument of risk management and environmental policy, and should be set by each country to protect the health of its citizens. The standards set in each country will vary according to specific approaches to balancing risks to health, technological feasibility, economic considerations and other political and social factors. This variability will depend on the country's level of development, capability in air quality management and other factors. The guidelines recommended by WHO

acknowledge this heterogeneity and recognize in particular that, in formulating policy targets, governments should consider their own local circumstances carefully before using the guidelines directly as legal standards.

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Part 1

Application of air quality guidelines for policy development and risk reduction

1. Sources of air pollution

Roy M. Harrison

Summary

Air pollutants may be either emitted into the atmosphere (primary air pollutants) or formed within the atmosphere itself (secondary air pollutants). Apart from the physical state of pollutants (such as gaseous or particulate matter) it is important to consider the geographical location and distribution of sources. The local, urban, regional and global scale of air pollution can be distinguished, depending primarily on the atmospheric lifetime of specific air components.

Primary air pollutants include sulfur dioxide, oxides of nitrogen, carbon monoxide, volatile organic compounds, and carbonaceous and non-carbonaceous primary particles. Some sources can be categorized on a geographical scale (point, line or area sources). Properties of a variety of sources such as road transport, stationary combustion sources and natural sources are described. Secondary air pollutants arise from chemical reactions of primary pollutants in the atmosphere, often involving natural components of the environment such as oxygen and water. Prominent secondary pollutants in the air include ozone, oxides of nitrogen and secondary PM.

For primary air pollutants, emission inventories are (often in combination with dispersion models) a powerful tool for predicting air quality. They can, for example, be used to model local, regional and global conditions and observe spatial and temporal trends in emissions. Receptor modelling is an alternative method that uses measurements of air quality, frequently in combination with simultaneously measured meteorological data, to recognize and quantify the contributions of specific characteristic source types to air pollutant concentrations. For secondary air pollutants, the mode of their formation makes it difficult to readily include them in emissions inventories or receptor modelling. Nevertheless, it is possible to estimate formation rates of secondary pollutants per unit volume of atmosphere per unit time.

Introduction

Basic definitions

Before discussing in detail the sources of air pollutants it is necessary to establish a few basic principles that will place the information on sources in context. Air pollutants may be either emitted into the atmosphere or formed within the atmosphere itself.

Primary air pollutants

Primary air pollutants are those that are emitted into the atmosphere from a source such as a factory chimney or exhaust pipe, or through suspension of contaminated dusts by the wind. In principle, therefore, it is possible to measure the amounts emitted at the source itself. This is relatively straightforward in terms of the factory chimney or vehicle exhaust pipe; it becomes very much more difficult when considering diffuse sources such as wind-blown dusts. When such sources are added together they comprise an emissions inventory of primary sources, as described below.

Secondary air pollutants

Secondary air pollutants are those formed within the atmosphere itself. They arise from chemical reactions of primary pollutants, possibly involving the natural components of the atmosphere, especially oxygen and water. The most familiar example is ozone, which arises almost entirely from chemical reactions that differ with altitude within the atmosphere. Because of this mode of formation, secondary pollutants cannot readily be included in emissions inventories, although it is possible to estimate formation rates per unit volume of atmosphere per unit time *(1)*.

Another important distinction must be made in relation to the physical state of a pollutant.

Gaseous air pollutants

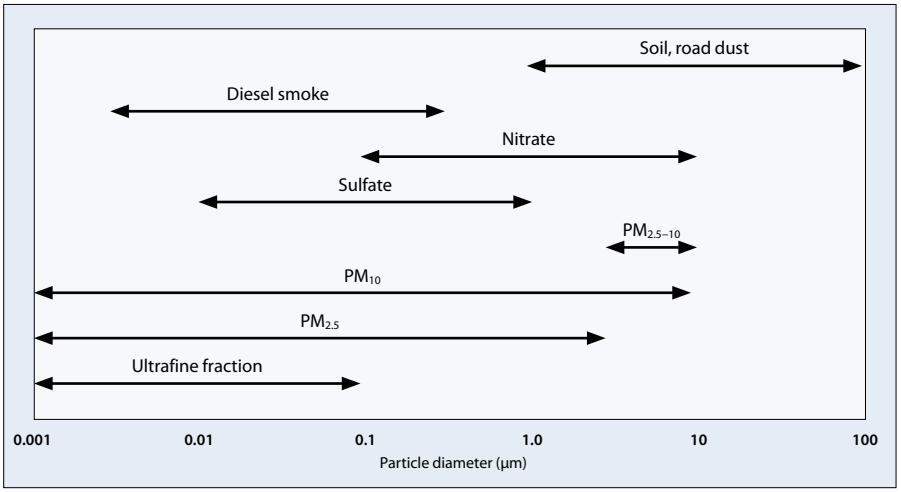
Gaseous air pollutants are those present as gases or vapours, i.e. as individual small molecules capable of passing through filters provided they do not adsorb to or chemically react with the filter medium. Gaseous air pollutants are readily taken into the human respiratory system, although if water-soluble they may very quickly be deposited in the upper respiratory tract and not penetrate to the deep lung.

Particulate air pollutants

Particulate air pollutants comprise material in solid or liquid phase suspended in the atmosphere. Such particles can be either primary or secondary and cover a wide range of sizes. Newly formed secondary particles can be as small as 1–2 nm

in diameter (1 nm = 10^{-9} m), while coarse dust and sea salt particles can be as large as 100 μm (1 μm = 10^{-6} m) or 0.1 mm in diameter. However, the very large particles have a short atmospheric existence, tending to fall out rapidly through gravity and wind-driven impaction processes. Thus in practice there are few particles in the atmosphere exceeding 20 μm in diameter, except in areas very close to sources of emission. Particulate matter can be separated from atmospheric gases by drawing air through a filter fine enough to retain the particles, or by accelerating air through a jet that fires them at a fixed plate, onto which the particles impact and are collected. Particulate air pollutants have very diverse chemical compositions that are highly dependent on their source. They are also diverse in terms of particle size. Fig. 1 illustrates the range of sizes (on a logarithmic scale) together with the ranges where certain important components are typically encountered. It shows also the PM_{10}, $PM_{2.5}$ and ultrafine particle fractions, which are typically those measured within the atmosphere for the purposes of health effects studies; the first two fractions are also used for compliance monitoring.

Fig. 1. Size range of airborne particles, showing the health-related ultrafine, $PM_{2.5}$ and PM_{10} fractions and the typical size range of some major components



In the context of discussing sources of air pollution, it is important to consider the geographical location and distribution of sources. Air pollution occurs on a range of spatial scales linked primarily to the atmospheric lifetime of the specific pollutants. Typical spatial scales are the following.

Local scale

Some pollutants, by virtue of their source or of having a very short atmospheric lifetime, are only encountered in appreciable concentrations close to where they are emitted. Examples are mainly rather esoteric chemicals, emitted from

specific industrial processes, that are not present at significant concentrations in the atmospheric background. Hydrogen fluoride is a pollutant with a relatively low general background concentration in the atmosphere, which can be encountered in high concentrations close to brickworks and other industrial sources. 1,3-Butadiene is an example of a pollutant with a very short atmospheric lifetime (typically of the order of an hour in daytime) that is encountered at elevated concentrations only rather close to its source, in this case mainly road traffic. In less developed countries, poorly controlled household and neighbourhood sources, often involving the burning of biomass fuels, cause serious local pollution.

Urban scale

Pollutants from urban sources, such as nitrogen oxides and carbon monoxide generated by road traffic, tend to be present at high concentrations throughout the city and at significantly reduced concentrations in adjacent rural areas. Their atmospheric lifetimes are not long (typically hours) and therefore concentrations in the remote background atmosphere tend to be very low (except in the case of carbon monoxide, which is more persistent). In countries such as China, coal burning may cause severe urban pollution with smoke and sulfur dioxide. Urban processes are discussed in detail by Fenger *(2)*.

Regional scale

Pollutants in the form of fine particles (<2.5 μm diameter, but not ultrafine particles) and some gas-phase pollutants such as ozone have atmospheric lifetimes of days or even weeks, which permit them to be transported on a regional scale. Pollutants such as sulfate particles and ozone readily travel thousands of kilometres in a process known as long-range transport, crossing national boundaries in doing so. Fine aerosols (particles) of black carbon arising from the burning of fossil fuels and biomass are also capable of long-range transport.

Hemispheric and global scales

Some pollutants, and especially those associated with greenhouse warming effects (carbon dioxide, nitrous oxide and methane) have atmospheric lifetimes of years and are therefore capable of distribution throughout a hemisphere and ultimately globally. In these cases, concentrations are often only marginally higher close to sources compared to the regional background, unless the sources emit very large quantities.

Primary pollutants

Primary pollutant formation mechanisms

To understand the sources and source inventories for air pollutants it is helpful to know the mechanisms of formation and release of the common air pollutants.

Sulfur dioxide

By far the main source of sulfur dioxide is the combustion of fuels containing sulfur. Fossil fuels, most notably coal and oil, contain varying amounts of sulfur according to their source but typically between 1% and 5%. On combustion, the sulfur in the fuel is converted almost quantitatively to sulfur dioxide. Nowadays in developed countries, much of the sulfur is removed from motor fuels in the refining process and from stack gases prior to emission. Sulfur is most abundant in the less volatile fractions of crude oil and hence shipping, which burns residual fuel oil, can be a very high emitter of sulfur dioxide. The sintering process used in metal smelting, which involves roasting metal sulfide ores in a stream of air, can also be a major mechanism of sulfur dioxide production. In less developed countries, however, unabated burning of coal and the use of fuel oils and automotive diesel with a higher sulfur content are major sources of sulfur dioxide.

Oxides of nitrogen

In a process parallel to that of sulfur dioxide production during fuel combustion, nitrogen in fuels is converted to oxides of nitrogen in the combustion process. Coal is the most important fuel in this context, as oil and gas contain much lower levels of nitrogen. However, there is a further process in which atmospheric nitrogen and oxygen are combined during high-temperature combustion to form oxides of nitrogen. This occurs in all high-temperature combustion processes and explains why road traffic and electricity generation tend to be among the predominant sources of these gases. The majority of nitrogen oxides formed through this route are emitted as nitric oxide. A smaller amount, typically 5% of the total, is emitted as primary nitrogen dioxide, while the major proportion of atmospheric nitrogen dioxide is a secondary product of atmospheric chemistry (see page 25).

Carbon monoxide

This is a gas formed during the incomplete combustion of carbon-containing fuels. While complete combustion leads to the formation of carbon dioxide, most combustion systems involve some fuel-rich regions in which a proportion of carbon is oxidized only to carbon monoxide. The most important example is the combustion of petrol in road vehicles.

Volatile organic compounds (VOC)

VOC comprise a very wide range of hydrocarbons, oxygenates, halogenates and other carbon compounds existing in the atmosphere in the vapour phase. The predominant source is typically through leakage from pressurized systems (e.g. natural gas, methane) or evaporation of a liquid fuel such as benzene from the fuel tank of a vehicle. However, combustion of fossil fuels and incineration processes also give rise to combustion emissions containing some unburned or partially burned fuel fragments that are emitted in the form of VOC. The exhaust

pipe of a vehicle may therefore be as important as the fuel tank as a source of VOC emissions. Organic solvents, used for example in paints and adhesives, are designed to disperse in the atmosphere to allow the active ingredients to dry.

Carbonaceous particles

The particles emitted from burning fossil fuels and biomass, for example in diesel and petrol engines, are typically composed largely of carbon, both in the elemental form and as organic compounds of low volatility. The elemental carbon is in the form of microcrystalline graphite formed from the build-up of carbon-containing free radicals into polycyclic aromatic structures within the flame. When these build only relatively small molecules they are emitted as polycyclic aromatic hydrocarbons, an important pollutant in their own right often associated with airborne particles *(3)*. If larger graphite structures are created in the flame, these will be emitted as particles of elemental carbon. Such combustion systems also tend to emit hydrocarbons of low volatility, deriving for example from lubricating oils, and these will typically condense on to the carbon particles. Carbon present within organic compounds, rather than as elemental carbon, is referred to as organic carbon.

Non-carbonaceous primary particles

An important source of non-carbonaceous particles is fly ash, which comprises particles largely of mineral material freed from a fuel such as coal in a combustion source and carried into the atmosphere with the flue gases. Purely mechanical processes such as quarrying can also create fragments of rock small enough to become suspended in the atmosphere and, as mentioned above, the action of the wind can suspend particles of soil and dust from land surfaces into the atmosphere. Construction and demolition activity can be an important source of coarser particles *(4)*, even in a street canyon where traffic emissions typically dominate.

Types of source

Before considering how inventories of emissions are constructed, it is valuable to consider the types of source responsible for air pollutant emissions. There are many ways of categorizing sources, and this section explores some of the main subdivisions and their characteristics. One of the main distinctions frequently drawn is between *stationary* and *mobile* sources.

This is a fairly obvious distinction whereby road vehicles, railway trains, ships, etc. comprise the mobile sources while industrial and household emissions, etc. comprise the stationary sources. In practice, however, air pollution science is rarely concerned with individual mobile sources but rather with the aggregated effects, such as that of all the vehicles travelling on a road within a defined period of time.

Consequently, a more useful categorization of sources is:

- point sources
- line sources
- area sources.

The term point source refers to sources that appear as individual points in the context of a gridded emissions inventory, which may resolve emissions spatially down to a 1 × 1-km scale or lower. Thus, for example, a power station might be considered as a point source even though it has more than one chimney. Individual industrial sites are typically considered as point sources of pollution unless the emissions occur from multiple sources within the site, probably at different heights. In such a case, each individual point of emission may need to be considered as a separate point source, particularly for dispersion modelling. Nevertheless, for the purposes of constructing emissions inventories, which tend to be concerned mostly with the masses of pollutant emitted as opposed to other characteristics of the release, individual company sites are often considered as point sources.

As stated above, air pollution science is rarely concerned with emissions from individual vehicles. Since road vehicles and railway trains typically travel along common routes, from the perspective of a source of emissions they form a line source. In the case of road vehicles, road networks are typically broken up into individual sections between junctions referred to as road links, and emissions from individual road links are added together to compile an inventory of total traffic emissions. Dispersion modelling uses formulae to calculate downwind concentrations from line sources that are modified from those used for point sources.

Many sources of emissions fit neither the point source nor the line source model. Rather, they are more diffuse and therefore spread over a significant spatial region. An example would be emissions from boilers used for space heating, whereby most homes would possess their own boiler, each of which is a small source of emissions. Rather than treating each as an individual point source, however, they are typically aggregated over an area, such as a grid square in an inventory or over a city, and treated as a uniform source within that area. This is justified provided they are distributed relatively homogeneously and no individual boiler makes such a large contribution that it requires modelling as an individual point source.

Properties of some types of source

Road transport

One of the major sources within any emissions inventory is road transport. The term is used to describe all road traffic emissions, irrespective of the size or usage of the vehicle. Emissions from road vehicles are typically thought of in terms

of the exhaust, though this is only part of the story (see below). Combustion of petrol or diesel fuel leads to the production of exhaust gas containing a range of potentially harmful pollutants. In many modern vehicles this passes through a control device, such as a three-way catalytic converter, before emission to the atmosphere. Pollutants emitted from the combustion of petrol or diesel fuels typically include carbon monoxide, oxides of nitrogen, VOC and suspended particles. Some countries still use lead additives in petrol and this generates an important air pollutant emission.

The amounts of carbon monoxide, nitrogen oxides, VOC and PM from road vehicles are closely regulated. There are essentially four sets of regulatory limits, i.e. those set by the US Environmental Protection Agency (USEPA), the State of California (which are more strict than those set by USEPA), the European Union (EU) and Japan. While these emission limits are set for vehicles sold within the boundaries of the standard-setting organization, they are typically also adopted by adjacent countries such as Canada (for American standards) and non-EU countries within Europe (for EU standards). The exhaust emission standards are set as limits in grams per kilometre or grams per mile of pollutant emitted over a standard driving cycle, within which a vehicle on a chassis dynamometer (rolling road) goes through a standard set of speed and load variations reflecting those experienced on the road. These are not normally evaluated for each individual new vehicle. Rather, a type approval process is used by which a manufacturer submits a small number of representative vehicles of a given type for testing. If these comply with the regulatory limits, the manufacturer gains approval for the sale of further vehicles of that type.

While exhaust emissions are often the most important emissions from a vehicle, they are far from being the only ones. Evaporative fuel emissions can also be important, especially from petrol vehicles, and these are measured and included in inventories of emissions. Far more difficult to account for, however, are the other non-exhaust emissions of PM from road vehicles that arise from sources such as the wear of brake components and tyres and the attrition of the road surface itself. Crude estimates have been made of the magnitude of these sources, which are included in many emissions inventories. However, road vehicles also cause the emission of particles by suspending particles from the road surface into the air, either through the turbulence in the wake of the vehicle or by the shear forces between the tyre and the road surface. These are far more difficult to account for and are not widely included in emissions inventories.

Stationary combustion sources

The burning of fossil fuels in stationary combustion plants is a further major source of pollutant emissions in most countries. High-temperature combustion is a source of nitrogen oxides, and also of sulfur dioxide if sulfur is present in the fuel. Fuel combustion also typically emits VOC, especially from coal and oil,

which are difficult to combust completely. While emissions from domestic heating and cooking can normally be considered as a ground-level source, those from combustion plants can occur at a wide range of altitudes, ranging from ground level for most domestic boilers to heights of more than 300 metres for large power station chimneys. Consequently, per kilogram of pollutants emitted, the impact on ground-level concentrations is very different: the ground-level source leads to far higher local concentrations than the elevated point source, but the elevated source influences areas much further afield because of the widespread dispersion of emissions.

Power stations have typically been among the greatest sources of combustion emissions but much is being done in the developed world to control the emissions from such sources. Examples are the use of burners producing low levels of nitrogen oxides and flue gas desulfurization of emissions from coal-fired power plants, in addition to the electrostatic precipitators normally fitted to limit emissions of PM.

Other industrial sources

A very wide range of industries and industrial processes lead to emissions of air pollutants, both the classical pollutants but also more esoteric pollutants that may be specific to a particular industrial process and may arise from leakage of an intermediate or product from a chemical plant. The measurement of emissions from chimneys and designed process vents is generally fairly straightforward, although it may require many measurements to obtain representative data. As well as the defined process emissions, however, many industrial operations also generate fugitive emissions. These are those arising from other, less well-defined sources, such as the wind blowing of raw materials from exposed stockpiles, and these are very much more difficult to quantify. A good example is that of secondary metal smelters, many of which have been operational for a large number of years and caused substantial contamination of the site and local area at a time when emissions were far less closely regulated than at present. For such a smelter it is likely that the impact of stack emissions on local air quality is very small, whereas there is a much larger impact on local air quality from resuspension of metal-containing soils and dusts by the action of the wind.

Intermittent and poorly defined sources

Globally, forest fires and deliberate biomass burning represent a major source of combustion emissions, including nitrogen oxides, carbon monoxide, VOC and PM. These are typically intermittent and often unplanned events that are very difficult to account for in any inventory. There are also smaller sources of this kind, which may be quite significant in national inventories. Concern over the health consequences of dioxin emission has led to a very tight regulation of known sources, especially incineration of refuse. This has highlighted the importance

of other sources, however, such as accidental fires and even planned events such as celebrations involving bonfires, as important sources of dioxin emissions. Because of their sporadic and very variable nature and the difficulty of measuring emissions, the magnitude of such sources (although included within emissions inventories) is rather uncertain. In less developed countries, burning of refuse and biomass-based fuels in clusters of poor households represent poorly defined and often intermittent sources that are very difficult to quantify.

Natural sources

Nature is an important source of many trace gases and particles within the atmosphere. One of the best known natural contributions to air pollution is the release of biogenic VOC from trees and other vegetation. These substances, which comprise isoprene, terpenes and other constituents, contribute to the production of both tropospheric ozone and secondary organic PM, and hence their impact on air quality through secondary pollutant formation can be very important. Globally, the natural production of sea spray and wind-blown soil is large, although its relevance to air pollution phenomena and health is likely to be very much smaller. In arid countries, dust storms can cause massive increases in PM concentrations, and wind-blown soils and dusts are one of the major particulate pollutants *(5)*.

Inventories of primary emissions

Emissions inventories are important tools and are the result of summing emissions from different sources across a geographical area, whether a grid square on a map or the entire area of a city, country or continent *(6)*. Emissions inventories are applicable only to emissions of primary pollutants; there is no straightforward way of including secondary pollutants. Typical applications of emissions inventories include local, regional and global air quality modelling and the surveillance of trends in emissions, both spatially and temporally. They are one of the key tools used by governments for air quality management.

Emissions inventories are compiled by summing the contributions of individual sources or source categories. Typically, for individual large point sources, measurement data will be available from which a direct estimate of the annual emission can be made. For smaller sources and particularly for area sources, however, it is more usual to calculate emissions using the following approach:

annual emissions = measure of activity × emission factor

In this context the measure of activity may vary considerably. In the case of space heating with gas, the most readily available statistic may be the annual domestic consumption of natural gas. For an industrial process, on the other hand, it may be the number of tonnes of cement manufactured. These activity statistics are then multiplied by an emission factor expressed in a compatible unit. Thus, following

the above examples, the emission factor for nitrogen oxides from domestic gas consumption would be expressed as grams of nitrogen oxides per cubic metre of gas consumed. In the case of cement manufacture, it would be as grams of PM per tonne of cement produced. Such emission factors are widely published by national and international agencies and are often specific to particular processes and applied technologies, including abatement. Thus emissions per tonne of cement manufactured would be different for a dry than for a wet manufacturing process, and different for an electrostatic precipitator than for a baghouse filter.

In the case of road vehicles, the vehicle fleet will need to be subdivided according to the type of vehicle, the fuel it uses, and its age or any abatement technology fitted. Emission factors are developed specifically for each of these elements. In conducting calculations for an inventory, it will be necessary not only to know the type of vehicle in each category but also the annual mileage of that type of vehicle or the proportion of the total mileage that it represents on a given road link. Inventories are becoming increasingly sophisticated in disaggregating vehicles according to their age and mileage, and also in allowing for high-emission vehicles with faulty abatement devices. It is not feasible to take data directly from type approval testing and assume that a vehicle that has been operating for, say, 100 000 km produces the same emissions as a new vehicle on a dynamometer test. Test cycles, although aiming to reflect the real world, do not always do so very well.

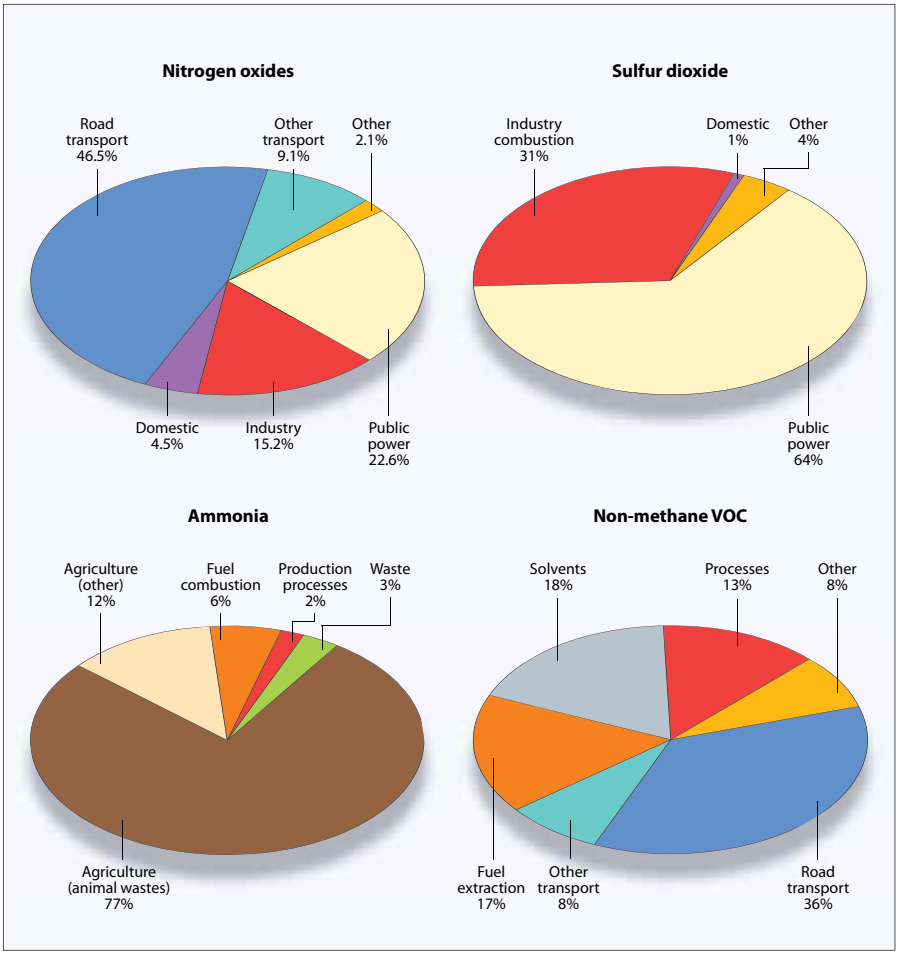
In compiling emissions inventories it is usual first to define a domain or spatial resolution, and second to define categories of activity into which emissions will be subdivided. The largest domain for most emissions inventories is the nation state, with many countries actively maintaining their own inventories of national emissions. Such data are valuable in setting targets for reducing emissions and in monitoring compliance with the requirements of international protocols such as the EU's National Emissions Ceilings Directive. International organizations and programmes such as the European Environment Agency and the European Monitoring and Evaluation Programme (EMEP) also maintain emissions inventories, in this case resolved into 50 × 50-km grid squares both at national and international levels. Many national inventories are more highly resolved; the United Kingdom initially developed urban inventories on a 1 × 1-km scale, but now has inventories at this resolution for many pollutants over the entire country.

There are different conventions for subdividing emissions, according to the activity responsible for them. One example is the SNAP 97 activity system used within the CORINAIR database by the European Environment Agency. The main categories used in the SNAP 97 system are listed in Box 1. Within these are numerous subcategories allowing the inventory user to investigate in greater depth the relative importance of different source types. Such inventories have many uses and are critical to the operation of global, regional and mesoscale (1–100 km) air quality models that require spatially disaggregated source input data.

Box 1. Main categories of air pollutant emissions used in SNAP 97

1 Combustion in energy and transformation industries
2 Non-industrial combustion plants
3 Combustion in manufacturing industry
4 Production processes
5 Extraction and distribution of fossil fuels and geothermal energy
6 Solvent and other product use
7 Road transport
8 Other mobile sources and machinery
9 Waste treatment and disposal
10 Agriculture
11 Other sources and sinks

Fig. 2. Emissions of nitrogen oxides, sulfur dioxide, ammonia and non-methane VOC from anthropogenic sources by sector, United Kingdom, 2001



Source: Air Quality Expert Group *(7)*.

Table 1. Contribution of road transport (RT) and other modes of transport (OT) to selected pollutant emissions by percentage of total emissions for the United Kingdom in 2000, the EU (EU15) in 1999, the EU accession countries (AC9) in 1999, the United States in 1999, various European countries in 1999 and Delhi, India in 1995

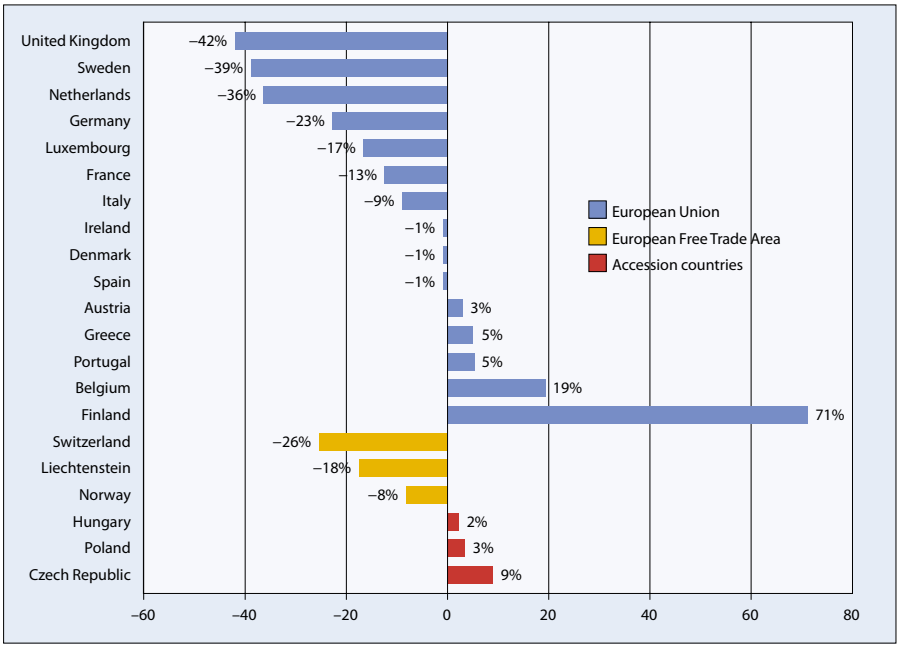
Area	Carbon monoxide		Nitrogen oxides		NM VOC		Sulfur dioxide		PM_{10}		$PM_{2.5}$		PM_1	
	RT	OT	RT	OT	RT	OT	RT	OT	RT	OT	RT	OT	RT	OT
United Kingdom	69	11	42	11	24	4	1	3	18	6	24	5	30	7
EU15	57	7	45	18	31	6	3	4	28[a]	11[a]		6.1[b]		
AC9			37	12	37	5	2	1						
United States	51	26	34	22	29	18	2	5	1.4[b]	2.2[b]	3.4[b]			
Austria	24.2		40.8		9.9		7.1		12.8					
Belgium	53.3		48.8		30.3		3.3		12.2					
Denmark	56.0		36.8		34.2	2.6	1.9	0.9	13.0					
Germany	53.0		50.9	11.9	20.4		3.1		16.1					
Finland	48.6		45.9		31.7	5			11.7					
France	41.5		51.4		25.5		4.9		11.3					
Italy	68.1		50.3		43.6		1.0		14.7					
Luxembourg	64.0		43.8	9–19	37.5		25.0		8.8					
Netherlands	60.5		41.8	6.5	36.0	5–12	4.9	1–3	14.7					
Spain	53.8		39.9	15	15.2		1.5		16.1					
Sweden	57.5		44.9		21.8	1.6	1.9	2.6	13.9					
Delhi, India	85.5		82.4		84.1		39.0		15.6[c]					

[a] Emissions of particulates assigned as primary and secondary fine particulates, of which 12% are considered primary PM_{10}.
[b] Direct emissions only (i.e. does not include fugitive dust).
[c] Based on inventory for total suspended particulates.
Sources: Thomas & Harrison *(8)*; Goodwin et al. *(9)*; Goodwin & Mareckova *(10)*; US Environmental Protection Agency *(11)*; European Environment Agency *(12)*; Gurjar et al. *(13)*.

National inventories are also valuable in the following ways.

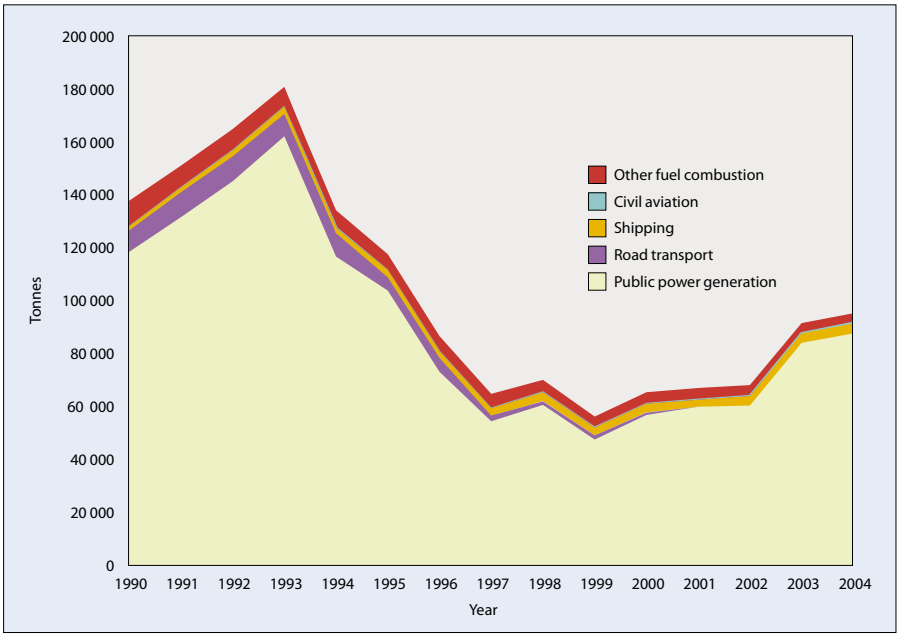
- They illustrate the relative importance of different source categories. For example, Fig. 2 shows national emission inventories for the United Kingdom for nitrogen oxides, sulfur dioxide, ammonia and non-methane VOC for 2001, showing widely different source profiles. Such information is useful in comparing the emissions between different countries. Table 1 shows, for a range of countries, the contributions of road transport and other modes of transport to emissions of selected pollutants by percentage of total emissions.
- They illustrate temporal trends in pollutant emissions. This is illustrated in Fig. 3, which shows the percentage change in PM_{10} emissions by country for Europe between 1990 and 2001, illustrating widely differing behaviour between different economies. Fig. 4 shows a time series by source category of sulfur dioxide emissions in Hong Kong, China. This shows successive rapid rises and declines in emissions, followed by a gradual increase between 1999 and 2004. It also shows that the dominant contribution due to electricity generation drives the temporal trends.

Fig. 3. Percentage changes in PM_{10} emissions in selected European countries between 1990 and 2001



Source: Air Quality Expert Group *(7)*.

Fig. 4. Temporal trends in sulfur dioxide emissions by source category in Hong Kong, China, 1990–2004



Source: Hong Kong Environmental Protection Department *(14)*.

- They allow one to compare the emissions profiles of different geographical areas. For example, when emissions inventories for major urban areas are compared with national inventories, it is typical for road traffic to be seen to play a much greater role in the emissions of cities than of whole countries. This behaviour is also reflected in the air quality measurements within cities. Fig. 5 shows a map of emissions of nitrogen oxides from road transport in London in 1999. The influence of road traffic is clearly seen, first in terms of a substantial gradient in emissions between the heavily trafficked central areas and the less trafficked suburban regions of the city, and second through the clear delineation of major road links. The most obvious one is the M25 motorway, which takes an orbital route around the city and hence appears to provide a boundary to the figure. Major arterial routes are also visible on the map, despite the fact that they cover only a small proportion of the 1 × 1-km grid squares into which the map is resolved.

Receptor modelling of pollutants

Emissions inventories, in combination with dispersion models, are a powerful tool for predicting air quality. Receptor modelling is an alternative method, used most frequently in relation to emissions of PM. This method uses the measurements of air quality itself, often in combination with simultaneously measured meteorological data, to recognize and quantify the contributions of specific characteristic source types to air pollutant concentrations. In the case of PM, multi-component chemical analyses of consecutively collected air samples allow recognition of components that co-vary in time and therefore have the same source. Typically some 6–10 individual source types can be identified through their chemical profiles. Table 2 illustrates the source apportionment of PM in

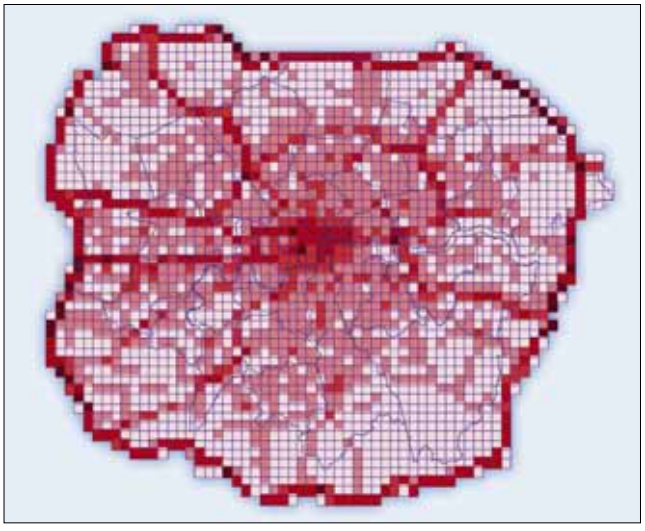


Fig. 5. Emissions of nitrogen oxides from road transport in London, 1999

Source: Air Quality Expert Group *(7)*.

Table 2. Average percentage contributions of the sources of coarse and fine particles at three sites in Bangladesh

Source profile	Dhaka (city centre)	Dhaka (semi-residential area)	Rajshahi
Coarse particles			
Sea salt	9.41	4.45	12.7
Soil dust	48.7	43.0	44.1
Road dust	–	7.30	14.2
Two-stroke engine	12.9	3.78	–
Metal smelter	–	1.12	–
Motor vehicle	23.4	40.2	23.2
Resuspended/fugitive lead	2.29	–	–
Construction	3.20	–	5.87
Fine particles			
Road dust	–	19.4	5.29
Soil dust	1.00	10.2	1.88
Biomass burning/brick kiln	37.5	11.9	50.4
Sea salt	–	1.00	13.9
Metal smelter	–	9.96	–
Two-stroke engine	2.41	9.36	–
Motor vehicle	43.0	38.2	28.5
Resuspended/fugitive lead	3.32	–	–
Unknown source	12.7	–	–

Source: Begum et al. *(15)*.

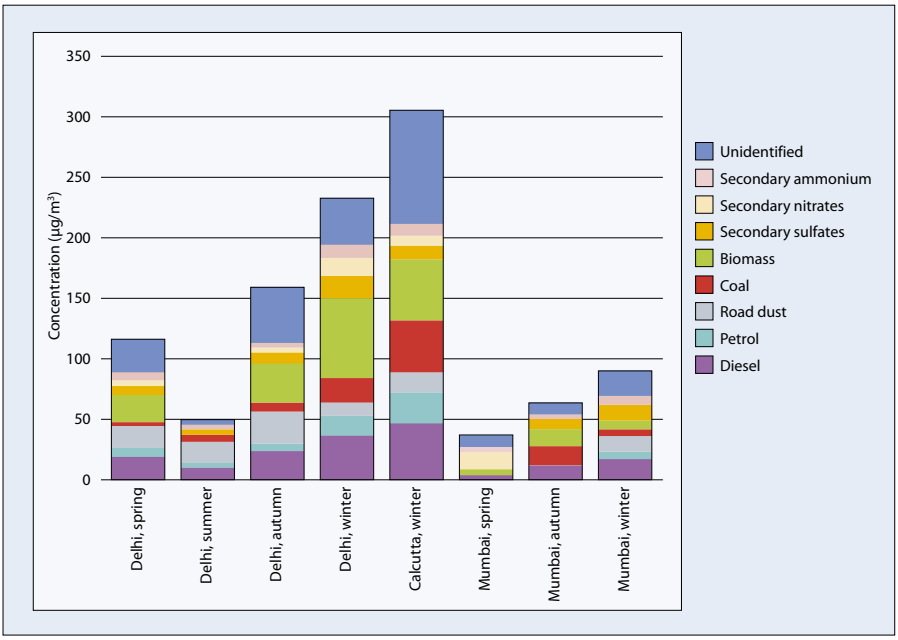
Bangladesh as determined in a receptor modelling study *(15)*, and Fig. 6 illustrates the results of a receptor modelling study of $PM_{2.5}$ in three Indian cities: Delhi, Calcutta and Mumbai. These contrast with results from most developed countries in showing large contributions from biomass burning, coal combustion and road dust. In developed countries, road dust is seen mainly in the coarse particle fraction and makes little contribution to $PM_{2.5}$.

Secondary pollutants

Introduction

As mentioned above, a number of important air pollutants arise predominantly through formation within the atmosphere itself. These arise as a result of atmospheric chemical reactions, and this section outlines the important reaction processes as well as giving some indication of their implications for pollutant formation.

Fig. 6. Results of receptor modelling of $PM_{2.5}$ in three Indian cities



Source: World Bank *(16)*.

The oxides of nitrogen/ozone system

As mentioned above, emissions of oxides of nitrogen occur predominantly in the form of nitric oxide, which typically comprises around 95% of nitrogen oxides from a combustion source. The pollutant of far greater concern in relation to human health is nitrogen dioxide (NO_2). The main pathway of conversion is via reaction with atmospheric ozone (O_3), which is present in the background atmosphere from a range of sources, including atmospheric transport from the stratosphere. There is also a pathway by which this chemistry can be reversed, with nitrogen dioxide breaking down as a result of absorption of sunlight to form nitric oxide (NO) and an oxygen atom (O), which reacts with an oxygen molecule (O_2) to re-form ozone. The three reactions are as follows:

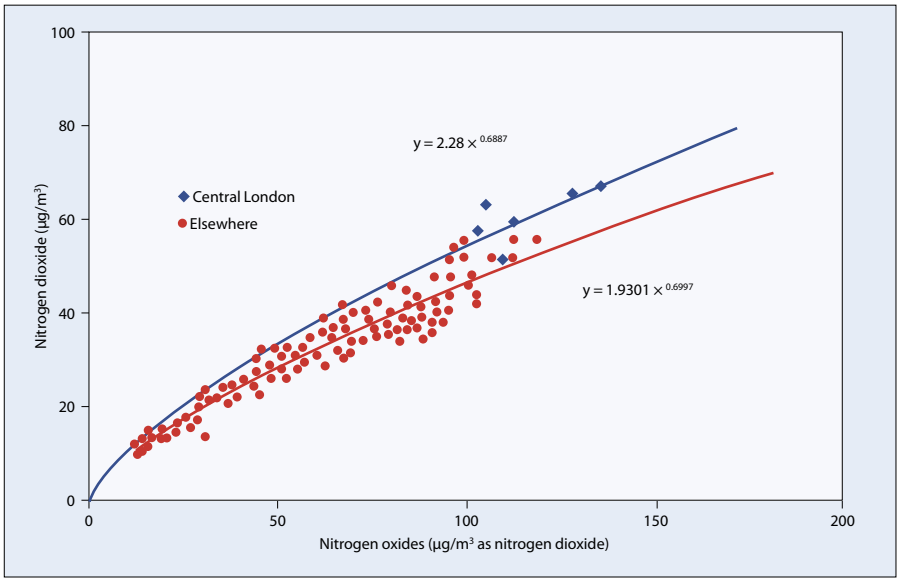
$$NO + O_3 \rightarrow NO_2 + O_2 \quad (1)$$

$$NO_2 + h\upsilon \text{ (sunlight)} \rightarrow NO + O \quad (2)$$

$$O + O_2 \rightarrow O_3 \quad (3)$$

Since each of these reactions is relatively fast, an equilibrium (the photostationary state), containing amounts of all three components, is quite rapidly established. Since reaction 2 depends on sunshine it becomes ineffective at night, and if there is sufficient ozone present reaction 1 can convert all nitric oxide to nitrogen dioxide, which often occurs in rural areas. In a highly polluted environment there is

Fig. 7. Relationship between annual mean concentrations of nitrogen oxides and nitrogen dioxide measured at background sites in the United Kingdom, 1998–2001, showing central London separately from other cities



Source: Air Quality Expert Group *(17)*.

unlikely to be sufficient ozone to complete the conversion and ozone concentrations, particularly at night in winter, may well fall to zero.

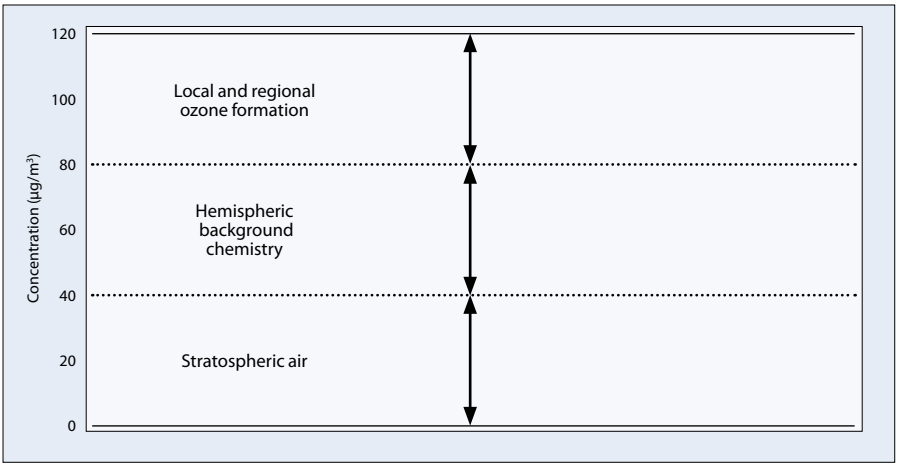
This chemistry has obvious implications for the control of nitrogen dioxide concentrations. Fig. 7 shows a typical relationship between annual mean concentrations of nitrogen dioxide and nitrogen oxides at an urban location in the United Kingdom. The relationship is curvilinear and reduction of high concentrations of nitrogen oxides leads to a far less than commensurate reduction in nitrogen dioxide. Consequently, very large reductions in emissions of nitrogen oxides may be needed to achieve compliance with air quality objectives for nitrogen dioxide.

Sources of ground-level ozone

Ozone is a secondary pollutant with three rather distinct sources within the lower atmosphere (see Fig. 8). There is a low background, probably less than half of the concentration currently encountered in the northern hemisphere, which arises from downward transport of ozone formed in the stratosphere by the photolytic breakdown of oxygen, where its presence is essential to filtering harmful ultraviolet light before it reaches the lower atmosphere (troposphere).

Ozone also forms in the troposphere as a result of atmospheric chemical reactions. The simple cycle shown in reactions 1–3 will not produce appreciable amounts of ozone, since as soon as it forms in reaction 3 it can readily be broken

Fig. 8. Typical source contribution to ozone concentrations measured on a polluted day at a mid-latitude location in the northern hemisphere



down in reaction 1. The situation is different, however, when there is bright sunshine and chemically reactive hydrocarbons are present. In this situation, oxidation of the hydrocarbons can lead to the formation of transient, highly reactive species known as peroxy radicals. In a polluted atmosphere, peroxy radicals react with nitric oxide and oxidize it to nitrogen dioxide:

$$\mathbf{NO + RO_2\ (alkyl\ peroxide) \rightarrow NO_2 + RO} \qquad \mathbf{(4)}$$

In doing so, the peroxy radical has converted nitric oxide to nitrogen dioxide without consuming an ozone molecule. Therefore, when reaction 4 is added to reactions 1–3 it can readily be appreciated that high concentrations of ozone can build up as long as peroxy radicals continue to be created. For a fuller account of the chemistry, the reader is referred to Harrison *(18)* or Monks *(19)*.

The creation of ozone can occur on both short and longer timescales. The longer timescales involve reactions in the remote atmosphere, for example over the oceans, where low concentrations of nitrogen oxides interact with methane and carbon monoxide (peroxy radical sources) to increase the hemispheric background of ozone, probably to about double that which prevailed in the pre-industrial era. The reactions are relatively slow but are important because of the large availability of the long-lived methane and carbon monoxide in the remote atmosphere. In more polluted atmospheres, as typified by Los Angeles but applying to many parts of the world, there is an abundance of more reactive hydrocarbons arising from anthropogenic emissions. In the presence of high concentrations of nitrogen dioxide and bright sunshine, high ozone concentrations can form relatively rapidly, leading to substantial pollution. While this is best known in the context of large cities such as Los Angeles and Mexico City, it also

occurs on a larger regional scale in areas such as western Europe, where the emissions from many cities combine together to form a highly polluted atmosphere in which ozone forms and is transported over long distances. The presence of peroxy radicals and their involvement in reaction 4 will also allow the creation of high concentrations of nitrogen dioxide, which far exceed those predicted by the photostationary state (reactions 1–3). One consequence of reaction 1 in polluted cities is that ozone concentrations within the city itself are often lower than those in the surrounding countryside, because fresh nitric oxide emissions from traffic suppress high concentrations of ozone entering in air from the surrounding countryside.

Secondary particulate matter

In some parts of the world, secondary particles can represent up to 50% of the total concentration of particles in the air. They comprise three main components. The first is sulfate, which arises from the atmospheric oxidation of sulfur dioxide and leads initially to the formation of sulfur trioxide, which rapidly condenses with water to form sulfuric acid. In regions with low ammonia emissions, sulfuric acid comprises the major form of sulfate. In many places, however, there are ample emissions of ammonia, which neutralizes the sulfuric acid to form solid particles of ammonium sulfate. Nitrogen dioxide is also oxidized in the atmosphere (typically faster than sulfur dioxide) to form nitric acid, which is present in the air as a vapour. Nitric acid, however, tends to react either with ammonia or with materials such as calcium carbonate or sodium chloride, leading to the formation of solid particles of nitrate. When these are in the form of ammonium nitrate, the formation process is appreciably reversible:

$$\mathbf{HNO_3\ (nitric\ acid) + NH_3\ (ammonia) \leftrightarrow NH_4NO_3\ (ammonium\ nitrate)} \qquad \mathbf{(5)}$$

Ammonium nitrate can dissociate back to nitric acid and ammonia, a process favoured by high temperature and low relative humidity. There can therefore be important diurnal and seasonal fluctuations in the amounts of ammonium nitrate in the air.

The third major form of secondary PM is secondary organic aerosol (SOA). This comprises oxidized organic compounds formed in the atmosphere by reactions of VOC. Biogenic VOC such as α-pinene emitted by trees are highly reactive in this context, and in some areas provide a very significant source of SOA. Anthropogenic VOC emissions are also capable of atmospheric oxidation, forming species of lower volatility that condense to form SOA.

Typically, the formation of secondary aerosol is relatively slow, taking a day or more. Consequently, the airborne concentrations of species such as sulfate tend to be rather uniform over quite large distances. In the case of nitrates and SOA, the formation processes are more rapid, and in the case of ammonium nitrate may be reversible, and therefore higher spatial gradients are to be expected.

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2. Global ambient air pollution concentrations and trends

Bjarne Sivertsen

Summary

Air quality measurements over the last decade have revealed air pollution problems in many of the major urban areas of the world, with some cities in developing countries currently facing the greatest challenges. Some typical ranges of concentrations of the four indicator pollutants found in a selection of cities around the world are summarized in Table 1.

Table 1. Ranges of annual average concentrations (μg/m³) of PM_{10}, nitrogen dioxide and sulfur dioxide and one-hour average maximum concentrations of ozone for different regions, based on a selection of urban data

Region	Annual average concentration			Ozone (1-hour maximum concentration)
	PM_{10}	Nitrogen dioxide	Sulfur dioxide	
Africa	40–150	35–65	10–100	120–300
Asia	35–220	20–75	6–65	100–250
Australia/New Zealand	28–127	11–28	3–17	120–310
Canada/United States	20–60	35–70	9–35	150–380
Europe	20–70	18–57	8–36	150–350
Latin America	30–129	30–82	40–70	200–600

The highest concentrations of the "classical" indicators such as PM_{10} and sulfur dioxide are found in Africa, Asia and Latin America. The highest levels of secondary pollutants such as ozone and nitrogen dioxide are measured in Latin America and in some larger cities and urban airsheds in the developed countries.

Trends in air quality development differ in respect of the four indicator pollutants. In Europe, PM_{10} levels had decreased by the end of last century but have tended to rise again, which may be partially explained by changing weather conditions. Even though large Asian cities have seen a slight reduction in PM_{10} levels over the last few decades, PM (PM_{10} and $PM_{2.5}$) is still the major air pollutant in Asia. Many of the large cities in Latin America, as well as Mexico City, still experience high levels of PM.

Sulfur dioxide levels have fallen in most parts of the world, including ▶

- substantial declines in Europe, China and the United States and to a more moderate extent in larger cities in Asia and Latin America.

Average national nitrogen dioxide concentrations have generally not declined, except in the United States. Since the principal sources of some secondary pollutants such as nitrogen dioxide and ozone are traffic-related, there is growing concern about rising levels in fast-growing cities with large numbers of vehicles. Data from Asian cities show a high year-to-year variation in nitrogen dioxide and ozone levels that currently renders trend analyses inconclusive.

As with nitrogen dioxide, ozone concentrations generally do not show a tendency to fall. Overall, the hemispheric background concentration of tropospheric ozone is increasing. Rising concentrations have been recorded for North American and European cities, and levels exceeding WHO's 2000 guideline values have been reported from cities in Mexico, Latin America, Africa, Australia and Europe.

One of the trends predicted to lead to increasing air pollution levels is the high rate of urbanization in countries where most of the population is on low income. It is expected that the rapid growth in urban populations will lead to a dramatic increase in vehicle numbers combined with inexpensive solutions for daily commuting, more frequent use of older and two-wheeled vehicles, poor car maintenance and other developments that increase air pollution.

Assessment of air quality based on available monitoring data

Which pollutants are addressed?

Ambient air pollution consists of a highly variable and complex mixture of different substances, which may occur in the gas, liquid or solid phase. Several hundred different components have been found in the troposphere, many of them potentially harmful to human health and the environment. Institutions such as environmental agencies around the world have developed a core set of air pollution indicators and criteria pollutants, which have been widely used to characterize air quality.

The assessment in this chapter is based mostly on data from monitoring of health-related air pollutants and focuses on four indicators of air pollution:

- PM, measured as particles with an aerodynamic diameter <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$)
- nitrogen dioxide
- sulfur dioxide
- ozone.

These indicators have been selected for the purpose of identifying typical air pollution concentrations. This selection, however, does not imply that other substances do not pose a considerable threat to human health and the environment at levels present in urban and industrialized areas around the world.

These four indicator pollutants are linked by complex atmospheric chemistry. Air pollution exists as a complex mixture and effects attributed to ozone, nitrogen dioxide, sulfur dioxide or PM may be influenced by the underlying toxicity of the full mixture of air pollutants. Also, various sources such as cars or power plants emit mixtures. Processes in the atmosphere further transform these pollutants to new compounds. For example, ground-level ozone is a secondary pollutant produced by the interaction of sunlight with nitrogen dioxide and VOC, as described in detail in Chapters 1 and 11.

Only a small number of parameters are usually measured in order to characterize the mixture; these parameters are then used as indicators in epidemiological studies. The lack of monitoring data sometimes impairs the possibility of identifying the most relevant indicator for different health endpoints *(1)*.

Assessment of air quality is conducted by national or local authorities in many countries. In some regions, such as Europe, international harmonization both of monitoring and of data exchange takes place. However, there is currently no such data exchange system covering other regions. Thus the information presented later in this chapter is based on selected data only, published independently and not in a harmonized way. The data illustrate patterns and trends in pollution but cannot be considered to provide a comprehensive global overview of air quality.

Measurement methods, and quality assurance and quality control

Instruments for measuring air pollutants may vary greatly in complexity and price, from the simplest passive sampler to the most advanced and expensive automatic remote monitoring system based on light absorption spectroscopy of various kinds.

Relatively simple equipment is usually adequate for determining background levels, estimating long-term average concentrations and observing trends. Passive samplers may also be adequate for undertaking simple screening studies. For the complete determination of air pollution distributions and relative source impacts and the operation of warning systems, however, more complex and advanced monitoring systems are needed. Also, when data are needed for verification of model performance, expensive monitoring systems are usually needed.

The accuracy of the air quality data and their representativeness in space and time are important for the quality of the assessments produced from the data. Data quality objectives are set, so that when they are fulfilled one can use the data confidently for the purposes for which the monitoring objectives have been set *(2)*.

In Europe the criteria that guide the quantification of data quality objectives are defined such as to permit:

- comparison of air quality across Europe;
- detection, over a reasonable period, of the trends in air quality in Europe as well as in each area where stations are located; and
- assessment of exposure.

Data quality objectives may also include specifications of accuracy, precision, area of representativeness and temporal coverage. Setting quality objectives and following a well-defined quality assurance and quality control (QA/QC) programme are essential for obtaining good quality data and comparable information. The measurement methods used and information concerning data quality requirements have not always been reported and controlled. Data quality may thus vary from one city to another and from region to region.

Representativeness of data

Information about the ambient air pollution levels have been based on measurements representative for different types of area and microenvironment, such as:

- traffic, near roads and in streets;
- urban areas, representative for the kilometre scale inside the urban airshed; and
- rural areas, away from local sources representative for residential areas.

The selection of representative measurement sites, as well as the use of different measurement methods, has made the interpretation and comparisons of the data difficult. Concentration levels presented in this book must thus be looked on as indicative of the air quality to be expected in different urban areas, in different regions and on different continents. Fig. 1 illustrates typical average concentrations of nitrogen dioxide, PM_{10} and ozone in rural, urban and traffic environments in Europe.

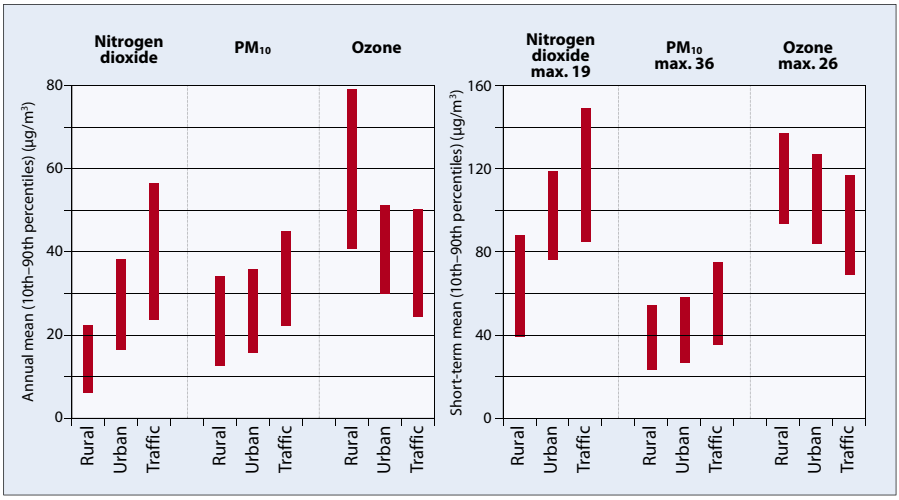
The ranges of concentration shown in Fig. 1 illustrate the variability in concentrations between different measurement sites, different environments and different cities. Sources of PM_{10}, nitrogen dioxide and other pollutants are normally of local origin, and concentrations often increase the closer one is to the source. For ozone, the picture is more complicated owing to chemical reactions involved in the build-up of ground-level ozone concentrations. Various factors independent of the air quality may affect the data, and therefore it is important to have information about site locations, measurement methods and data quality assurance procedures when evaluating air pollution levels in different cities and countries.

Megacities of the world

Air pollution in megacities around the world has been an issue for several years. At the turn of the century there were 24 megacities each with more than 10 million

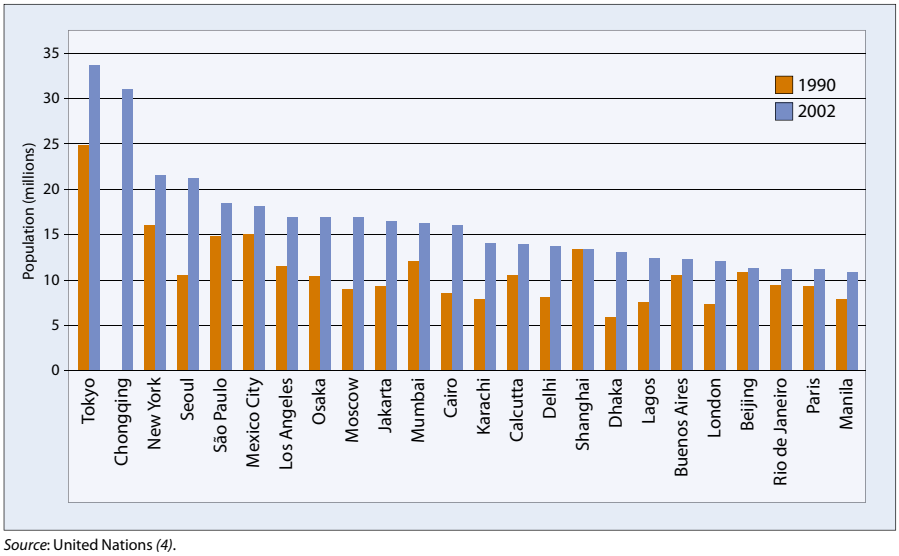
inhabitants (Fig. 2). Four of these had more than 20 million inhabitants in 2002. Twelve of these megacities are located in Asia, four in Latin America and two in Africa: Cairo in Egypt and Lagos in Nigeria. According to the World Bank some African cities are growing by more than 10% annually.

Fig. 1. Ranges of concentrations at rural, urban and traffic stations in Europe, based on data for 2001



Max 19: 19th highest one-hour average concentration of nitrogen dioxide measured during the year.
Max 36: 36th highest daily PM_{10} concentration during the year.
Max 26: 26th highest 8-hour mean within one day, calculated from hourly running 8-hour average concentrations of carbon monoxide.
Source: Larssen S *(3)*.

Fig. 2. The 24 megacities in the world with populations (including suburbs) exceeding 10 million in 2002

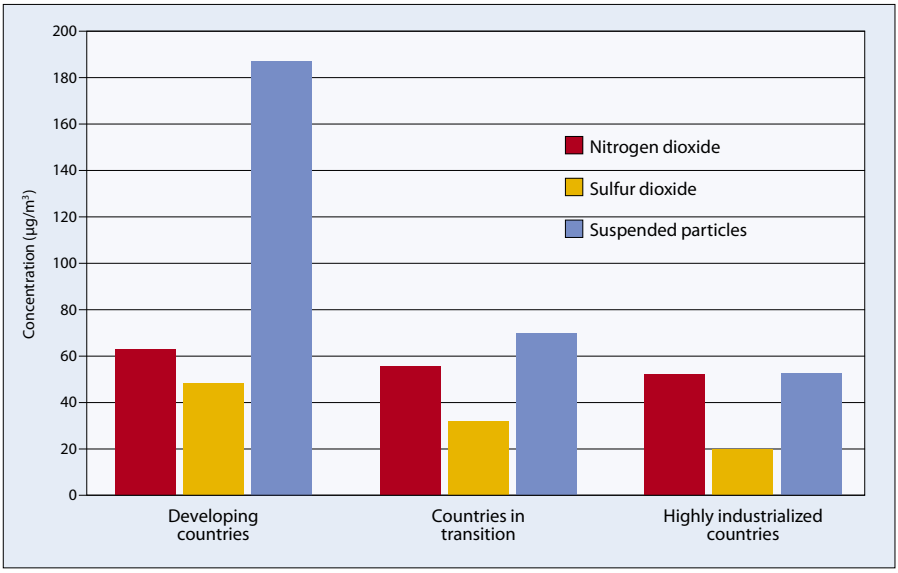


Source: United Nations *(4)*.

In many megacities, such as Beijing, Calcutta, Mexico City, Rio de Janeiro and Cairo, high levels of PM constitute a major problem. Los Angeles and Mexico City are still recording high concentrations of ozone and nitrogen dioxide. Several other cities, such as Karachi, Mumbai and Lagos, are fighting multiple air pollutants that exceed national standards.

Air pollution levels are normally higher in developing countries than in highly developed industrialized countries. This is illustrated by the typical annual average concentrations of nitrogen dioxide, sulfur dioxide and suspended particles presented in Fig. 3.

Fig. 3. Typical annual average concentrations of nitrogen dioxide, sulfur dioxide and suspended particles in different parts of the world



Source: United Nations Human Settlements Programme *(5)*.

PM levels indeed present serious problems in the developing countries. PM_{10} concentrations have been reported from countries such as India and Pakistan to be 4–5 times international air quality limit values.

Urban air quality problems

The serious consequences of exposure to high levels of urban ambient air pollution were made clear in the mid-twentieth century, when cities in Europe and the United States experienced air pollution episodes (such as the infamous 1952 London Fog) that resulted in many deaths and hospital admissions. Subsequent clean air legislation and actions reduced ambient air pollution in many regions. The winter smog problems associated with coal combustion that were common in some cities during the 1980s and early 1990s have been eradicated, and it is

now mainly emissions from traffic that pose the main threat to good air quality. The main sources for the present air pollution levels in western cities are traffic-related.

The previously frequent winter smogs comprising a mixture of sulfurous compounds and particles (soot) have in this way changed over the years. Suspended particles, and especially submicron particles, combined with secondary pollutants such as oxides of nitrogen and ozone, have become a major problem in the large urban areas around the world. At the same time, the populations of the rapidly expanding megacities of Asia, Africa and Latin America are increasingly exposed to levels of ambient air pollution that rival and often exceed those experienced in industrialized countries in the first half of the twentieth century *(6)*.

PM_{10} or respirable particulate matter

Up to now, the most frequently used indicator for suspended particles in the air has been PM_{10} (particles with an aerodynamic diameter <10 μm). An overview of typical annual average PM_{10} concentrations in selected cities around the world is presented in Fig. 4. The data selected for this presentation demonstrate that the general levels of suspended particles in Asia and Latin America are higher than those in Europe and North America. The annual average PM_{10} concentrations in the selected Asian cities ranged from about 35 μg/m^3 to 220 μg/m^3 and in Latin America from about 30 μg/m^3 to 129 μg/m^3, while in Europe and North America the typical range of annual average PM_{10} concentrations was 15–60 μg/m^3. About 70% of the cities selected from these regions had annual average PM_{10} concentrations above 50 μg/m^3.

In general, the highest concentrations of PM_{10} were reported from Asia. This region also experiences relatively high background concentrations owing to forest fires and local emissions of particles from the use of poor-quality fuels. A well-known springtime meteorological phenomenon throughout East Asia, causing the Asian dust cloud, originates from windblown dust from the deserts of Mongolia and China and adds to the general level of PM in the region.

Chinese cities experience very high airborne particle concentrations due to primary particles emitted from coal and biomass combustion and motor vehicle exhaust, as well as secondary sulfates formed by atmospheric chemical reaction from the sulfur dioxide emitted when coal is burned. Typical annual average PM_{10} concentrations were reported to be as high as 140 μg/m^3 in Beijing *(16)*.

In many areas of the world, massive and prolonged forest fires have caused significant increases in PM concentrations. During the approximately 2½ weeks of the large forest fires in California in 1987, PM_{10} concentrations as high as 237 μg/m^3 were measured *(17)*. In another fire in the United States, lasting 10 weeks, PM_{10} levels exceeded 150 μg/m^3 (24-hour average) 15 times, and on 2 days the levels exceeded 500 μg/m^3 *(18)*. In the 1997 fires in south-east Asia, PM_{10} levels as high as 930 and 421 μg/m^3 were measured in Sarawak and Kuala Lumpur,

respectively, while levels in Singapore and southern Thailand were somewhat lower *(19)* (see Chapter 10 for more examples).

PM_{10} levels in Europe have been presented for 2002 based on data from more than 1100 monitoring stations in 24 countries, including some 550 urban areas *(3)*.

In urban areas the average concentrations were:

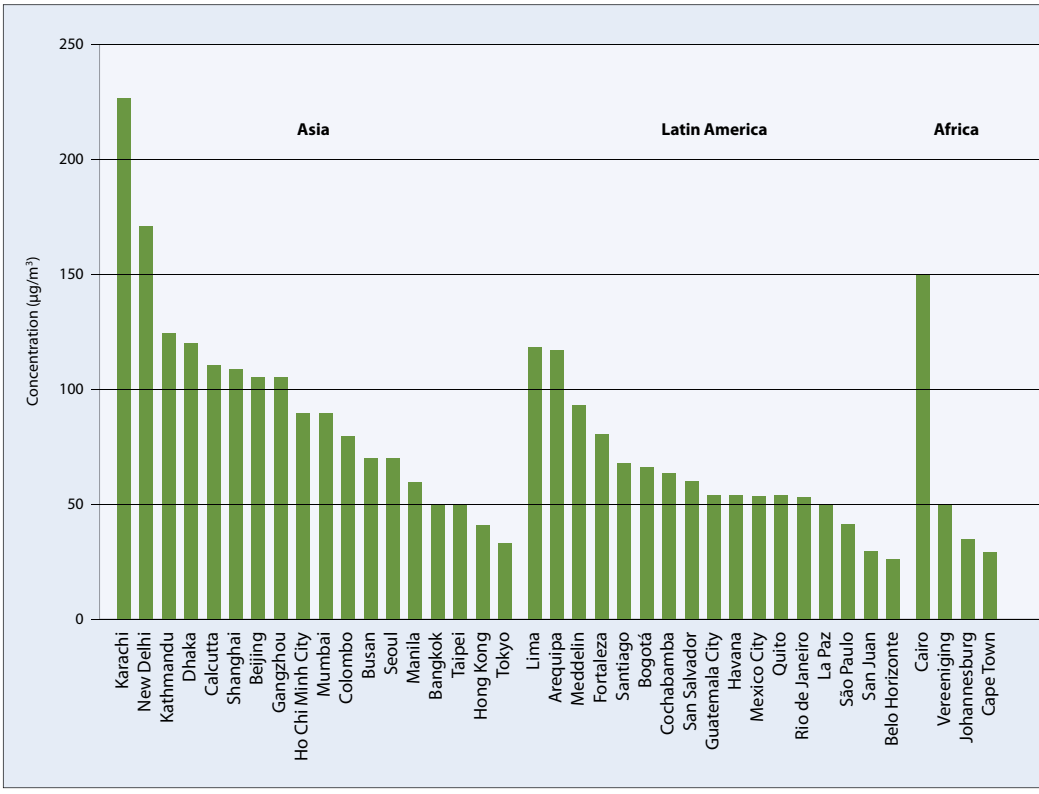
- annual average 26.3 μg/m^3 in urban background and 32.0 μg/m^3 in streets; and
- daily average (36th highest value) 43.2 μg/m^3 in urban background and 51.8 μg/m^3 in streets.

In rural areas the concentrations were:

- annual average 21.7 μg/m^3; and
- daily average (36th highest value) 38.1 μg/m^3 (141 stations).

The highest annual average concentrations measured exceeded 80 μg/m^3, while the highest daily average concentrations exceeded 150 μg/m^3.

Fig. 4. Annual average PM_{10} concentrations observed in selected cities worldwide

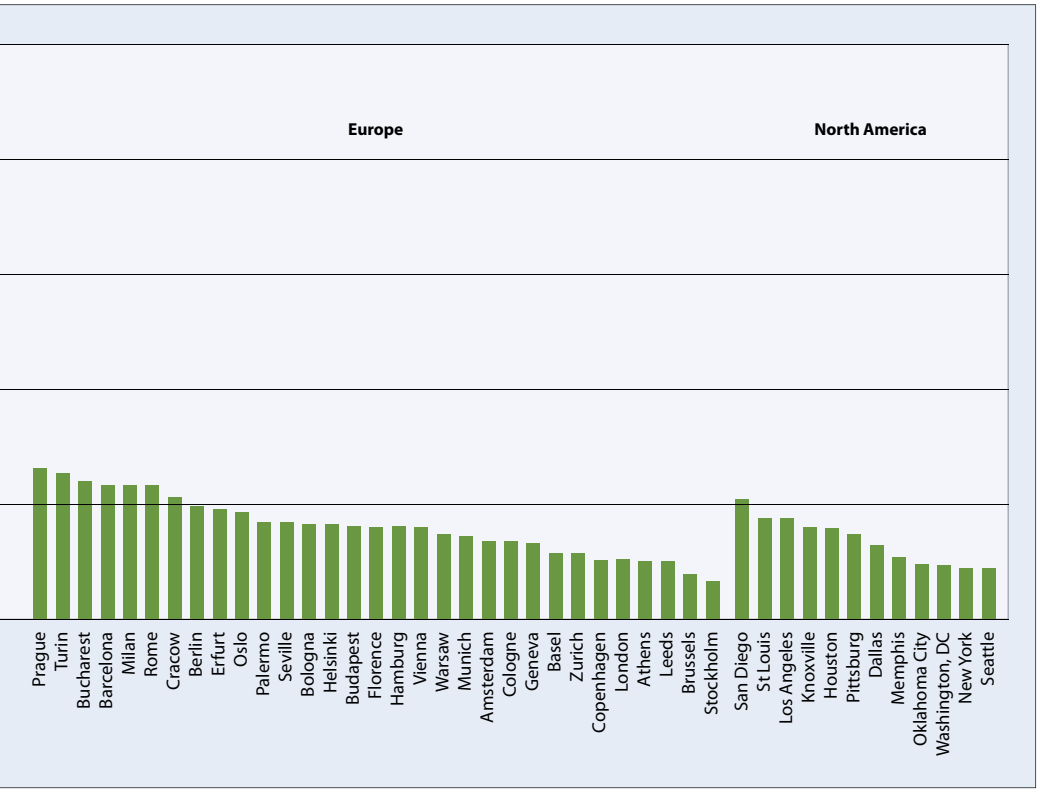


Sources: Bourotte et al. *(7)*; US Environmental Protection Agency *(8)*; Sivertsen & El Seoud *(9)*; Sivertsen et al. *(10)*; State Environmental Protection Agency *(11)*; CAFE *(12)*; Department of Environment and Heritage *(13)*; Department of Environmental Affairs and Tourism *(14)*; US Environmental Protection Agency *(15)*.

Concentrations of PM_{10} have been summarized for 17 selected cities in Latin America and the Caribbean region for 2000–2004 (Maisonet DM, personal communication, 2005). The results, indicate that annual average concentrations had a range of 30–118 μg/m^3. In most cities, PM levels in 2004 were lower than those measured in 2000.

Reports on air quality in Santiago de Chile are available for several years. The city is located in the middle of a valley and is surrounded by mountains. The winter months, April to September, are clearly more polluted than the summer months *(20)*. Typical average PM_{10} concentrations reached 90 μg/m^3 in 2003/2004. A wintertime study of fine particles in São Paulo, Brazil *(7)* showed average PM_{10} concentrations at 33 μg/m^3. The highest observed daily PM_{10} concentration was 89 μg/m^3. A report by the US Environmental Protection Agency on 340 cities nationwide *(8)* showed annual mean PM_{10} concentrations of 14–63 μg/m^3, with an overall national average of 26 μg/m^3. Toronto and Montreal in Canada reported annual average PM_{10} concentrations of 20–28 μg/m^3.

Large differences in reported PM_{10} concentrations are found in Africa. Well-developed cities such as Cape Town and Johannesburg in South Africa report



rather low annual average PM_{10} concentrations of around 30–40 μg/m³. In the greater Cairo area, however, the typical annual average concentrations in urban and residential areas ranged from 60 μg/m³ to 200 μg/m³. In industrial areas concentrations measured were between 200 μg/m³ and 500 μg/m³ *(9)*.

The natural background concentration of PM_{10} in Egypt is high owing to wind-blown dust from the desert areas. Based on local measurements, "background" PM_{10} concentration has been estimated at about 70 μg/m³. Towns in arid areas with surrounding deserts frequently receive a considerable amount of dust from wind-blown fine sand. In Cairo it was found that large fractions of the PM_{10} might be attributed to fine sand particles *(21)*. During air pollution episodes, the burning of agricultural and other waste also contributed.

Pollution in the Kathmandu valley was analysed based on data from March 2003 to February 2004. The PM_{10} concentration peaked at around 300 μg/m³ in December 2003 while in July and August it was around 120 μg/m³, showing that the valley experiences a winter dry period with high concentrations of particulates.

In Hanoi, the mean PM_{10} mass concentration at an urban site was measured at 38 μg/m³, twice the level measured at a rural site. In Ho Chi Minh City, the annual average PM_{10} concentrations measured at seven sites ranged from 50 μg/m³ to 130 μg/m³ *(10)*.

The air quality in cities in China is generally improving, even though two out of three cities in 2002 recorded PM_{10} levels above 60 μg/m³ *(11)*. The cities having relatively severe particulate pollution were mainly in northern China, in the central plains and in the eastern parts of Sichuan and Chongqing.

From Australia it has been reported that atmospheric particles resulting from seasonal wood smoke are of concern in some cities. Current efforts to educate the community on appropriate use of domestic wood heaters are likely to take a long time to show substantial benefit. The largest cities such as Sydney and Melbourne, however, reported annual average PM_{10} concentrations as low as 20–22 μg/m³ *(22)*.

$PM_{2.5}$, an indicator for fine particles

$PM_{2.5}$ is an important indicator of risk to health from particulate pollution, and might also be a better indicator than PM_{10} for anthropogenic suspended particles in many areas.

The ratio of $PM_{2.5}$ to PM_{10} has been reported from many cities worldwide. A study in 239 American cities *(23)* revealed $PM_{2.5}$: PM_{10} ratios of between 0.44 and 0.71, while studies in Cairo *(10)* indicated a ratio of around 0.5. In Santiago de Chile, average daytime values were between 0.4 and 0.6, with the highest ratios during the winter months *(24)*.

$PM_{2.5}$ concentrations depend on the type of source, distance from the source and wind speed. Natural PM sources can contribute significantly to $PM_{2.5}$

although less than they contribute to PM_{10}. The $PM_{2.5}$: PM_{10} ratio measured in African dust outbreaks over eastern Spain ranges from 0.4 to 0.8, but this rises to 0.7–0.9 in northern Spain *(25)*.

$PM_{2.5}$ and smaller fractions of PM are measured to a much lesser extent than PM_{10} in Europe. Data from 119 $PM_{2.5}$ measuring stations showed the $PM_{2.5}$: PM_{10} ratio to be 0.65 with a range of 0.42–0.82 *(12)*. The rural background concentrations of $PM_{2.5}$ in Europe seem to be in general quite uniform at between 11 μg/m³ and 13 μg/m³, and considerably lower than urban background levels (around 15–20 μg/m³), which in turn are lower than $PM_{2.5}$ annual averages at traffic sites (typical range 20–30 μg/m³).

The average $PM_{2.5}$ concentrations in the United States were 12.5 μg/m³ in 2002, with 90% of the sites having $PM_{2.5}$ levels <16 μg/m³ *(8)*.

Fine particles are responsible for most visibility problems in Asia. Recent measurements in the centre of Beijing show $PM_{2.5}$ concentrations averaging just over 100 μg/m³. The monthly average concentrations varied between 61 μg/m³ and 139 μg/m³. During air pollution episodes, daily mean $PM_{2.5}$ values can reach 300 μg/m³ *(26)*.

The highest daily $PM_{2.5}$ concentration measured in São Paulo, Brazil was 27 μg/m³, while the average $PM_{2.5}$ concentration in winter was 12 μg/m³ *(7)*.

Ultrafine particles

Ultrafine particles are usually formed by nucleation, which is the initial stage of the process by which gas becomes a particle. These particles are a few nanometres in size but can grow up to 1 μm, either through condensation (when additional gas condenses onto the particles) or through coagulation (when two or more particles combine to form a larger particle).

Over the last few years, an increasing number of studies have reported particle number concentrations for various locations and environments around the world *(27)*. In most cases for which particle size distributions have been reported, ultrafine particles (smaller than 0.1 μm) have comprised the dominant fraction.

Particle number concentrations in urban background environments range from a few thousand to some 20 000 particles per cm³. Close to roads or in tunnels, particle concentrations can reach and even exceed 10^5 particles per cm³. The actual levels depend in the first instance on traffic conditions on the road (traffic flow and mode), and also on meteorological conditions and the topography of the site.

A summary of selected measurements of ultrafine particles in urban and roadside environments around the world is presented in Table 2.

Ozone, a regional and global problem

Ozone in the lower part of the atmosphere (troposphere) is one of the most widespread global air pollution problems today. In and around urban areas, relatively

Table 2. Ultrafine particle number concentrations measured in urban and roadside environments

Location	Monitoring period	Average particle number concentration per cm^3	Reference
Barcelona, Spain	Not stated	1.23×10^4	Paatero et al. *(28)*
Birmingham, England	Not stated	1.8×10^5 (roadside)	Harrison et al. *(29)*
Brisbane, Australia	14–29 January 2004	~2.7×10^4 (roadside)	Holmes et al. *(30)*
Brisbane, Australia	1995 – April 1997	7.4×10^3 (urban)	Morawska et al. *(31)*
Copenhagen, Denmark	3–20 May 1999	$1.2 \times 10^5 – 2.0 \times 10^5$ (roadside)	Wåhlin et al. 2001 *(32)*
Detroit, USA	July 2002	1.9×10^4 (roadside)	Young & Keeler *(33)*
Erfurt, Germany	1991–2001	$1.04 \times 10^4 – 1.4 \times 10^4$ (roadside)	Kreyling et al. *(34)*
Helsinki, Finland	1999–2001	1.90×10^4 (urban)	(Hussein et al. *(35)*
Los Angeles, USA	Aug–Oct 2001	6.00×10^4 (roadside)	(Zhu et al. *(36)*
Rome, Italy	Not stated	$1.8 \times 10^5 – 3.5 \times 10^5$ (roadside)	(Paatero et al. *(28)*

Source: Morawska et al. *(27)*.

large gradients of ozone can be observed. Near strong emission sources of nitrogen oxides, where there is an abundance of nitric oxide, ozone is "scavenged" as it reacts with nitric oxide. As a result, the ozone concentrations are often low in busy urban centres and higher in suburban and adjacent rural areas. Ozone and some of its precursors are also transported long distances in the atmosphere and are therefore considered a transboundary problem. Thus, on a scale of tens of kilometres, regional observation networks provide the data from which these patterns of ozone can be examined.

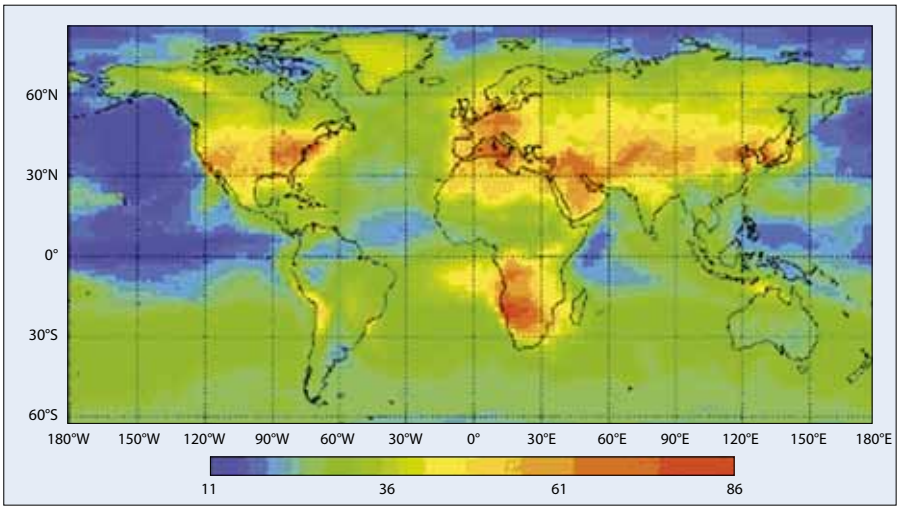
The photochemical formation of tropospheric ozone from increased concentrations of methane and carbon monoxide may also lead to a higher ozone level on a global scale *(37)*.

Fig. 5 shows model calculations of mean afternoon surface ozone concentrations for the month of July. Particularly noteworthy is pollution over industrial areas in the United States, Europe and Asia. In these areas, ozone is formed as a secondary pollutant when emitted precursor pollutants such as nitrogen oxides and VOC react under the action of sunlight.

Recent studies have shown that the hemispherical background concentration of tropospheric ozone is increasing *(37)*.

Surface ozone concentrations are usually assessed as short-term (1- to 8-hour) averages. The highest 1-hour average ozone concentrations measured in the most polluted cities are presented in Fig. 6.

Fig. 5. Mean afternoon (13:00 to 16:00) surface ozone concentrations calculated for the month of July



Source: Harvard University *(38)*.

There are more than 1000 ozone-monitoring sites in Europe, both in rural and in urban areas, with the majority of sites near local precursor emission sources. Nevertheless, the spatial resolution of the monitoring networks is in general insufficient, and documentation on the representativeness of the individual sites is poor *(39)*.

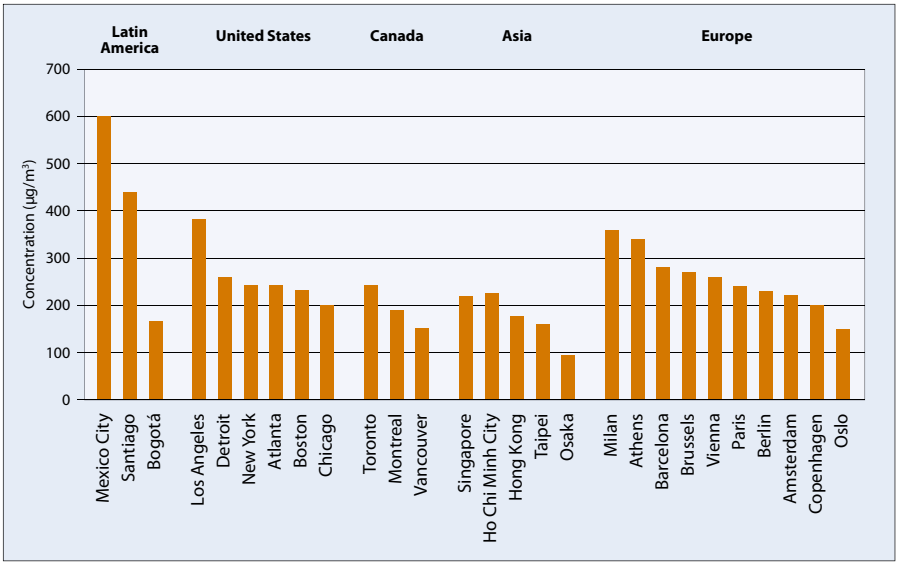
The surface distribution of ozone over Europe in the summer of 2003, as reflected by ozone observations reported to the European Environment Agency, indicate that there were exceptionally long-lasting and spatially extensive episodes of high ozone concentrations. These mainly occurred at the end of July and in the first half of August and covered those regions with the highest temperatures, as shown in Fig. 7.

A trend analysis covering the 12 years from 1993 to 2005 *(41)* showed that the average number of hours with an ozone concentration above 180 μg/m^3 (the EU information threshold) for any given monitoring site was higher in the summer of 2003 than in any of the previous years. Some of the Mediterranean cities recorded 1-hour average ozone concentrations above 300 μg/m^3.

High ozone concentrations also remain a major problem in the Americas. The highest concentrations of secondary pollutants, such as nitrogen dioxide and ozone, are still measured in the Los Angeles basin *(8)*. Large urban airsheds with poor ventilation, such as Los Angeles, Mexico City and Santiago de Chile, have experienced short-term ozone concentrations exceeding 400 μg/m^3.

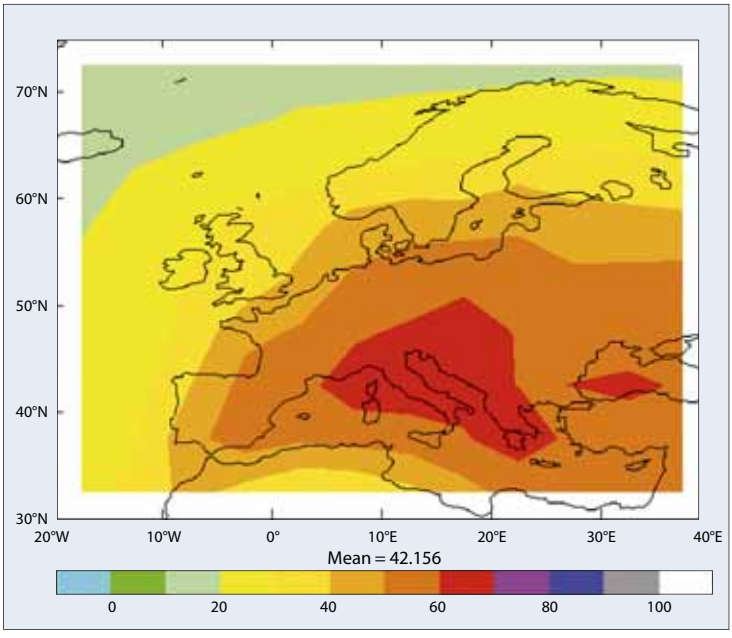
Observations in and around major urban areas show strong diurnal variations. Measurement in India reported significant diurnal cycles in the average ozone concentration, with an average maximum of 117 μg/m^3 in the peak at noon and

Fig. 6. Highest (1-hour average) ground-level ozone concentrations measured in selected cities



typical minimum of 23 µg/m^3 at sunrise. The average concentration of ozone was 53 µg/m^3 with a range of 3–135 µg/m^3 *(42)*. Similar results have been reported from Ho Chi Minh City, where the 99th percentile of hourly ozone concentration was 120 µg/m^3 *(10)*.

Fig. 7. Modelled surface ozone concentrations (ppb) over Europe during July for the years 2000–2009



Source: Derwent et al. *(40)*.

High concentrations of surface ozone have been observed as a result of regionally produced secondary pollutants in the Cairo region. Also, background tropospheric ozone at Ras Mohamed, at the southern tip of the Sinai Peninsula, shows high concentrations (especially in the summer) frequently exceeding 150 μg/m^3. In the urban area of Cairo, 120 μg/m^3 (8-hour average) was exceeded for more than 10% of the time during the year, and at Ras Mohammed for more than 15% of the time *(9)*.

In Australia, 8-hour ozone levels exceeded 120 μg/m^3 on some occasions in some areas and cities such as Sydney, Melbourne and Perth *(43)*. Measurements at 28 sites in Australia showed 1-hour average maximum concentrations ranging between 120 μg/m^3 and 310 μg/m^3 *(13)*.

Sulfur dioxide, traditionally from the burning of fossil fuel

Levels of sulfur dioxide have decreased markedly in most of Europe and North America and in many locations in Asia as well. The improvements in most member countries of the United Nations Economic Commission for Europe in the last few decades has been driven by various national and international regulations, including the Protocols under the Convention on Long-range Transboundary Air Pollution.

An overview of typical annual average sulfur dioxide concentrations reported from a selected number of cities in Asia, Africa, the Americas and Europe, based on data from 2000–2005, is presented in Fig. 8. About half of the cities reported annual average concentrations above 20 μg/m^3, while 50 μg/m^3 was exceeded in about 15% of the cities included.

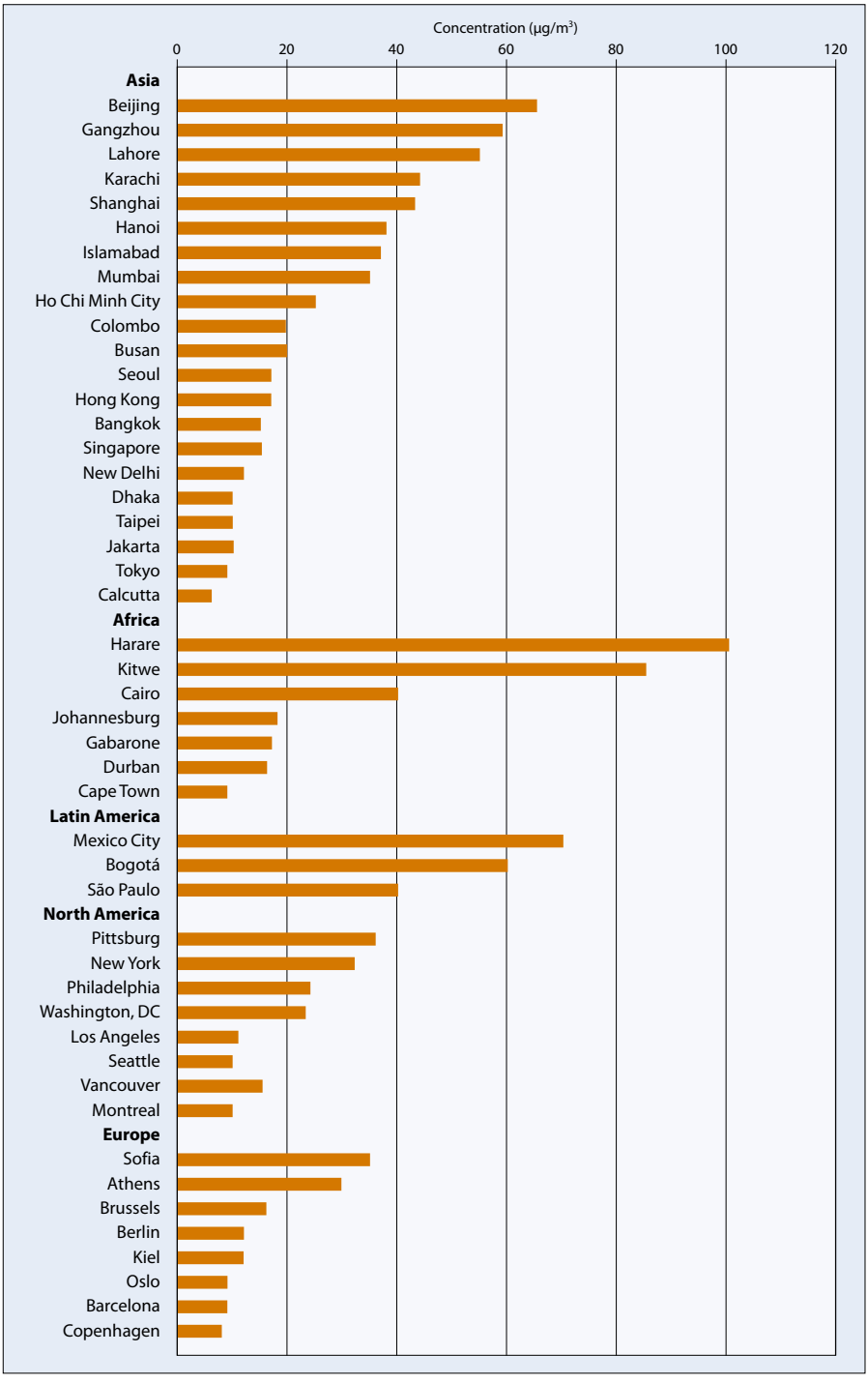
The highest sulfur dioxide concentrations are being recorded in some of the megacities in developing countries, although some large urban areas have fairly low concentrations. In February 2005, New Delhi reported weekly average concentrations of 5–10 μg/m^3, while Djakarta reported between 4 μg/m^3 and 24 μg/m^3 *(44)*.

Sulfur dioxide levels that are already high in some cities in China may increase further, owing to the continued use of coal as a key energy source. Air pollution concentrations are generally higher in northern Chinese cities than in the south. The average sulfur dioxide concentration in 2002 was 52 μg/m^3 *(45)*. The national average sulfur dioxide concentration in 2004 was 43 μg/m^3, and 22% of cities recorded annual average concentrations above 60 μg/m^3.

While typical annual average concentrations of sulfur dioxide in urban areas in developing countries are 40–80 μg/m^3, those in North America and Europe are 10–30 μg/m^3, and in cities in the EU 6–35 μg/m^3. Data from some individual measurement sites have indicated higher levels, however.

In Africa some of the urban areas, and especially industrial areas, still experience high concentrations of sulfur dioxide. Levels of sulfur dioxide were measured at 28 sites in Egypt *(9)*. Three locations in Cairo had more than 50 μg/m^3 as

Fig. 8. Annual average sulfur dioxide concentrations in 2000–2005 reported from selected cities worldwide



an annual average sulfur dioxide concentration. The annual average concentrations in other areas of Africa frequently exceed 50 μg/m^3 *(46)*. Weekly average concentrations in Zambia's copper belt (Nkana, Mufulira and Luanshya) were found to range from 167 μg/m^3 to 672 μg/m^3, the highest weekly average being 1400 μg/m^3 *(47)*.

Studies undertaken on the impact of the Selebi Phikwe copper smelter in Botswana show that there are large areas experiencing concentrations above 100 μg/m^3. Short-term measurements indicated 1-hour average concentrations of more than 1000 μg/m^3 *(48)*.

The City of Harare Health Department carries out routine air pollution monitoring at eight sites. Data available for 1995–2001 indicated that the typical annual average sulfur dioxide concentrations were about 100 μg/m^3 in 2001 *(49)*.

Also, some of the heavily industrialized areas in Europe may still be experiencing high levels of sulfur dioxide. In some cities in the north-western corner of the Russian Federation, close to large primary smelters, daily concentrations of sulfur dioxide exceed 1000 μg/m^3 *(50,51)*.

Nitrogen dioxide, a problem related mainly to mobile sources

The principal sources of nitrogen dioxide are traffic and to a lesser extent industry, shipping and households. High nitrogen dioxide levels, combined with ultrafine particles and other oxidants, have become one of the major air pollution problems in urban areas all over the world. Nitrogen oxides are one of the main components of the mixture of pollutants classically referred to as "photochemical smog".

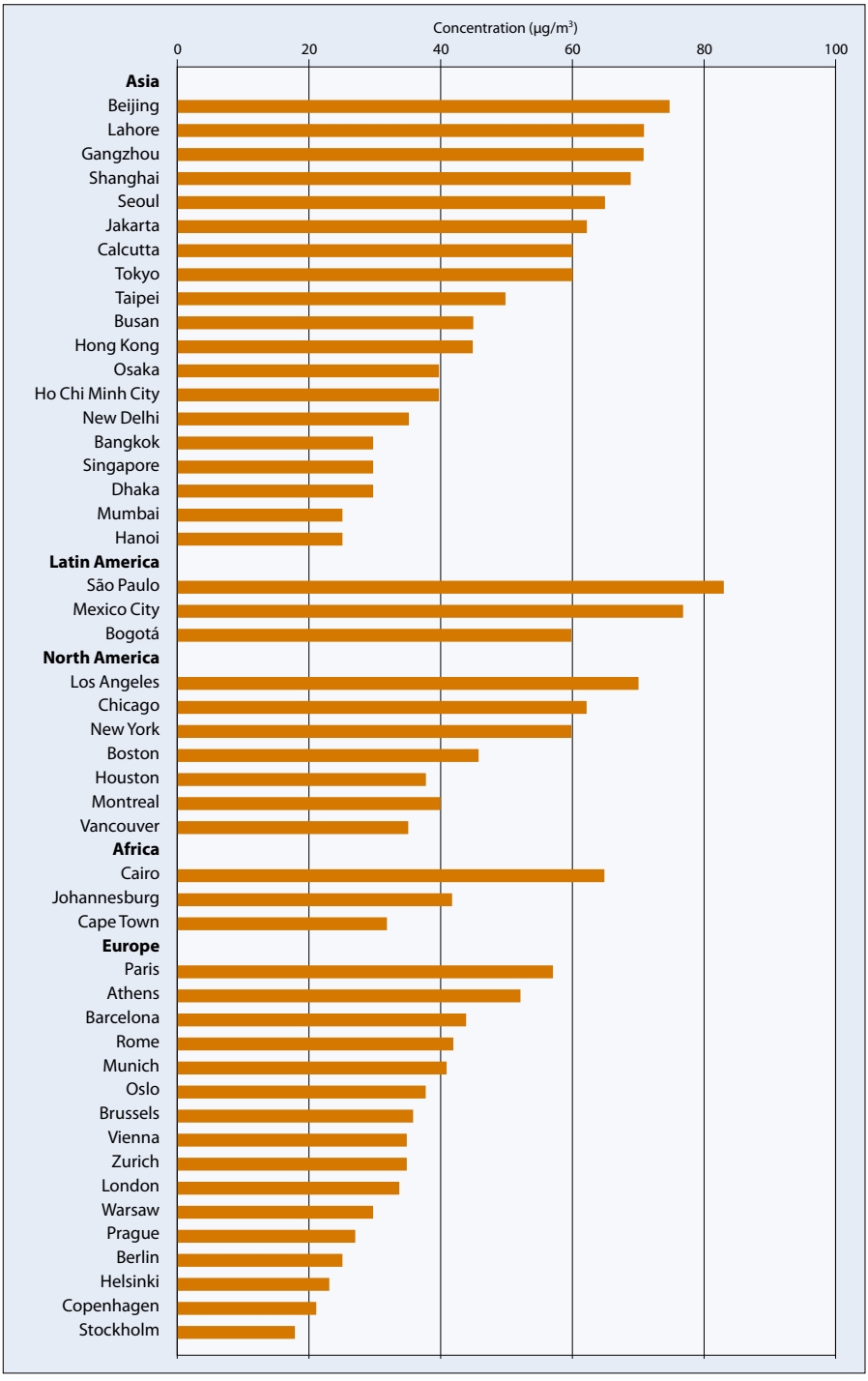
Rural background concentrations of nitrogen dioxide in industrialized countries have been measured at around 15–30 μg/m^3. In urban areas, nitrogen dioxide concentrations exceed 40 μg/m^3 as an annual concentration (WHO's 2000 air quality guideline) in many of the larger cities on all continents.

Short-term nitrogen dioxide concentrations may vary considerably within cities and from time to time during the day and night. Also, average concentrations depend on the distance of the measurement site from main roads. Fig. 9 summarizes the annual average nitrogen dioxide concentrations measured in selected cities around the world.

The annual average nitrogen dioxide concentrations in major European cities were reported in 2002 to range from 14 μg/m^3 in Iceland to 44 μg/m^3 in France. Stockholm reported annual average levels of 18 μg/m^3 while Paris reported 57 μg/m^3. Kerbside levels may be significantly higher: the 19th highest one-hour average nitrogen dioxide concentration in 2002 was estimated at 32 μg/m^3 in urban areas and 59 μg/m^3 at street stations *(52)*.

In the United States, the annual average nitrogen dioxide concentration estimated from measurements in 125 cities was 36 μg/m^3, while 10% of the cities had annual average concentrations exceeding 55 μg/m^3 *(53)*. In Mexico City, average

Fig. 9. Annual average nitrogen dioxide concentrations in 2000–2005 reported from selected cities worldwide



concentrations in 2002 ranged from 27 μg/m^3 to 77 μg/m^3, with an average for 19 measurement sites of 51 μg/m^3 *(54)*.

Annual average nitrogen dioxide concentrations in Asian cities typically lie in the range 23–74 μg/m^3. In 2002, the average concentration in Calcutta was 77 μg/m^3 and in New Delhi 49 μg/m^3 *(55)*. Typical concentrations measured in New Delhi in February 2005 were 31–83 μg/m^3. In Jakarta, average nitrogen dioxide concentrations mapped using passive samplers showed levels of 20–70 μg/m^3 as a weekly average *(44)*. The peak daily concentration was 446 μg/m^3.

In the urban areas of Africa, traffic emissions have become the dominant source of nitrogen dioxide. Annual average concentrations in Cairo ranged between 25 μg/m^3 and 83 μg/m^3, while in the city's streets the concentrations were between 75 μg/m^3 and 83 μg/m^3 *(56)*.

Typical daily average nitrogen dioxide concentrations in South African cities such as Cape Town, Johannesburg and Vereeniging were 100–160 μg/m^3 *(14)*. Measurements at eight sites in Dar es Salaam, United Republic of Tanzania revealed that nitrogen dioxide concentrations ranged from 150 μg/m^3 to 350 μg/m^3 during daytime hours *(57)*. Data from 28 sites in Australia showed annual average nitrogen dioxide concentrations of 11–28 μg/m^3 *(13)*.

Trends in air quality

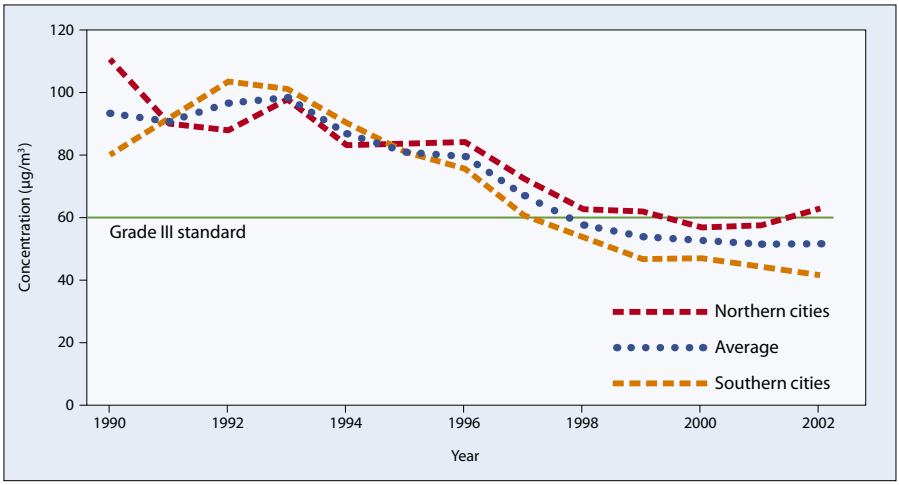
Many air pollution indicators have shown a downward trend during the last decade, the most obvious being the reduction of sulfur dioxide in most parts of the world. Nitrogen dioxide concentrations and the general levels of ozone, on the other hand, do not show the same declining tendencies.

Asia

In general, PM (PM_{10} and $PM_{2.5}$) is the main pollutant of concern in Asia. In cities with large and growing numbers of vehicles, however, there is increasing concern over levels of nitrogen dioxide and ozone. The aggregated data for nitrogen dioxide and ozone in Asian cities show considerable year-by-year variation, and the high variability of data across Asian cities indicates that further analysis is needed to arrive at a more logical representation of the trends of these two pollutants. Cities such as Singapore, Hong Kong, Shanghai, Beijing, Tokyo, Kuala Lumpur and Bangkok have developed light rail and mass transit systems to reduce the pressure on the roads and provide an opportunity to reappraise city-wide transportation plans *(58)*.

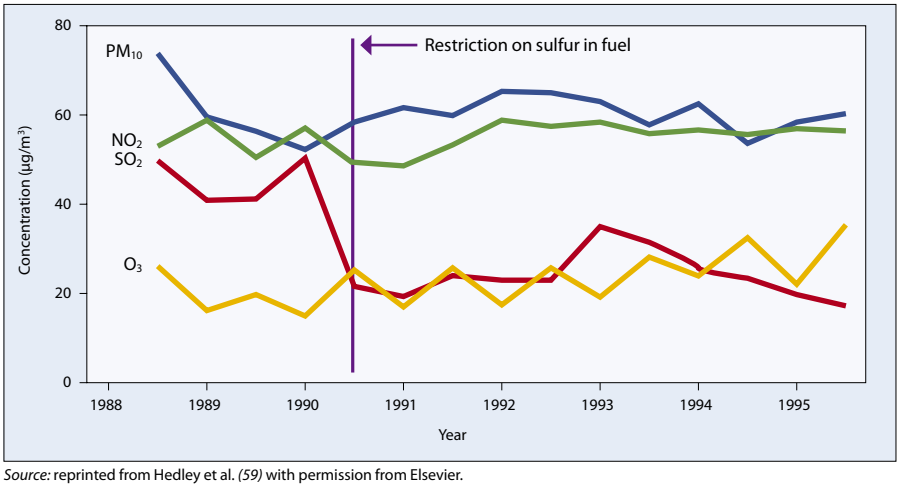
For sulfur dioxide, however, a downward trend is evident in Asian large cities such as Bangkok, Mumbai and Seoul. In Chinese cities, too, there has been a clear reduction in sulfur dioxide levels during the last ten years, as shown in Fig. 10. In general, air pollution in northern cities is more severe than in southern cities. The average sulfur dioxide concentration in China fell by 44.3% from 93 μg/m^3 in 1990 to 52 μg/m^3 in 2002 *(45)*.

Fig. 10. The development of annual average sulfur dioxide concentrations in Chinese cities from 1990 to 2002



Source: Hao & Wang *(45)*.

Fig. 11. Average concentrations of PM_{10}, nitrogen dioxide, sulfur dioxide and ozone at five Hong Kong monitoring stations



Source: reprinted from Hedley et al. *(59)* with permission from Elsevier.

The introduction of restrictions on sulfur in fuels is one of the reasons for the decline in sulfur dioxide concentrations. This is clearly seen in Fig. 12 showing ambient concentrations in Hong Kong, China, where restrictions were imposed from 1990. Furthermore, cleaner fuels such as natural gas, which contains less ash and sulfur, have replaced coal and high-sulfur oils. Also, light transport systems, as mentioned above, have contributed to this improvement in some cities.

A study by the Clean Air Initiative for Asian Cities, summarizing air quality data from 20 cities in Asia, shows that on average there has been a slight to

moderate reduction in pollution levels for sulfur dioxide and PM_{10} (Fig. 12) *(60)*. Also, total suspended PM decreased from 1992 to 2003.

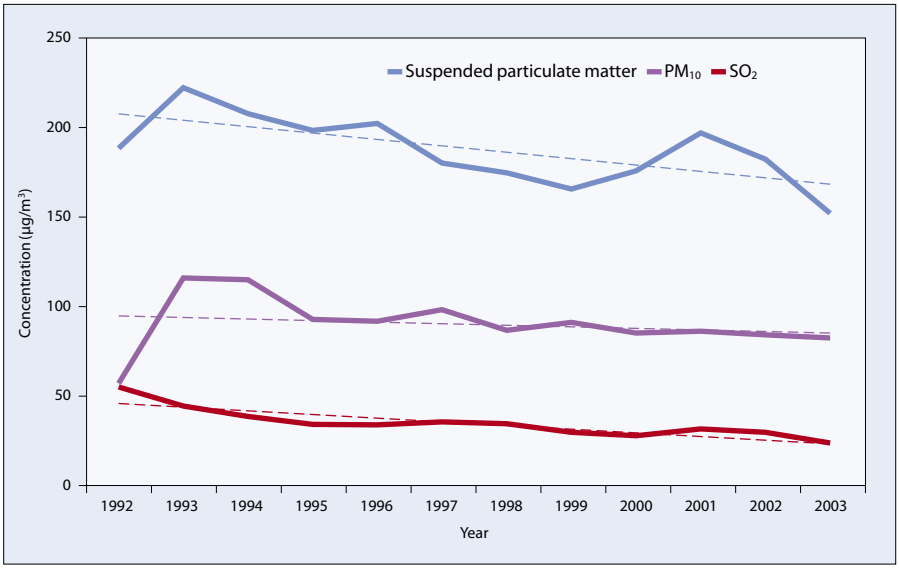
North America

Peak air quality statistics for six air quality indicators, based on data from 340 metropolitan areas in the United States, demonstrated a downward trend between 1993 and 2002, except for 8-hour average ozone concentrations. Out of 296 metropolitan statistical areas where ozone trends were estimated, only 36 showed significant upward trends *(15)*.

Nitrogen dioxide levels have decreased by 21% in the United States since 1983, a trend that is reflected in all regions of the country. Nationally, average nitrogen dioxide concentrations are now at the lowest levels recorded in the past 20 years. From 1993 to 2003, the annual average PM_{10} concentration in the United States fell by 13% and nitrogen dioxide concentrations by 11%. The 8-hour average ozone concentrations, however, increased by 4% over the same period. Sulfur dioxide concentrations the United States have fallen significantly: the annual average fell by 39% between 1993 and 2002, the largest drop being from 1994 to 1995 *(53)*.

Elevated ozone and $PM_{2.5}$ concentrations have been reported in southern Ontario, Canada during the smog season. Ozone measurements in Canada show that the annual 1-hour maximum concentration of ozone decreased from 1980 to 2003, although there was an increasing trend in mean concentrations of ozone during the same 24-year period.

Fig. 12. Trends in major pollutants in 20 Asian cities, 1992–2003



Source: Clean Air Initiative for Asian Cities *(60)*.

Europe

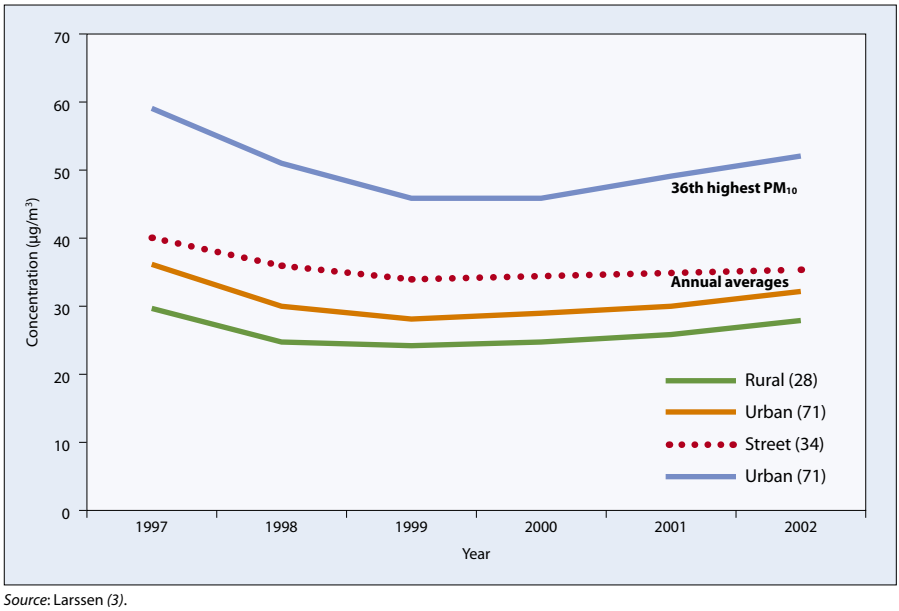
In Europe, the number of monitoring stations after 1997 was large enough to permit the trend analyses shown in Fig. 13. From 1997 to 2000, there was a downward trend in PM_{10}. The increase in PM_{10} levels since 2000 cannot easily be explained by the available data, although atmospheric modelling has strongly suggested that it is due to meteorological variations.

PM_{10} levels in Europe are dominated by a rural component. In most areas, the rural concentration is at least 75% of the urban background concentration and in some very densely populated areas, such as the Netherlands, the rural concentration is more than 90% of the urban background.

Background ozone concentrations measured at Zugspitze in Germany illustrate (Fig. 14) that regional concentrations across Europe increased between 1978 and 2002. Critical levels of ozone are being exceeded over large areas, and current levels need thus to be reduced further.

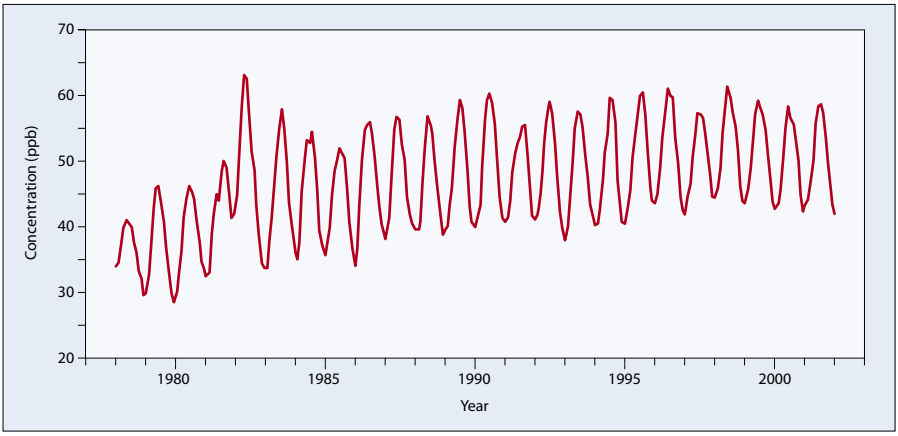
It has been suggested that intercontinental transport contributes significantly to European background ozone levels. There is a growing number of observational data indicating increasing hemispheric levels and intercontinental transport of ozone. Nevertheless, large gaps still remain in our understanding of intercontinental transport and its possible impact on air quality at ground level. Most of the evidence published concerns pollutant plumes in the upper troposphere, and there are relatively few conclusive observations from surface stations *(39)*.

Fig. 13. Annual average PM_{10} concentrations and the 36th highest daily PM_{10} concentration per year in Europe, 1997–2002



Source: Larssen *(3)*.

Fig. 14. Monthly mean ozone concentrations measured at Zugspitze, Germany since 1978



Source: Scheel *(61)*.

Latin America

Many of the large cities in Latin America still experience high concentrations of PM and secondary pollutants. The five million inhabitants of Santiago de Chile are exposed to high levels of air pollution during a significant portion of the year. Santiago ranks as one of the most polluted cities in the world. Air quality data, as presented in Fig. 15, show that there was a slight fall in PM_{10} concentrations until 2001; since 2001 the levels have increased again.

A downward trend in sulfur dioxide levels is evident in large Latin American cities such as Mexico City and São Paulo. In Mexico City, neither nitrogen dioxide nor sulfur dioxide concentrations exceeded annual average limit values after 2001. Nevertheless, ozone and PM still pose a severe problem in the city *(54)*.

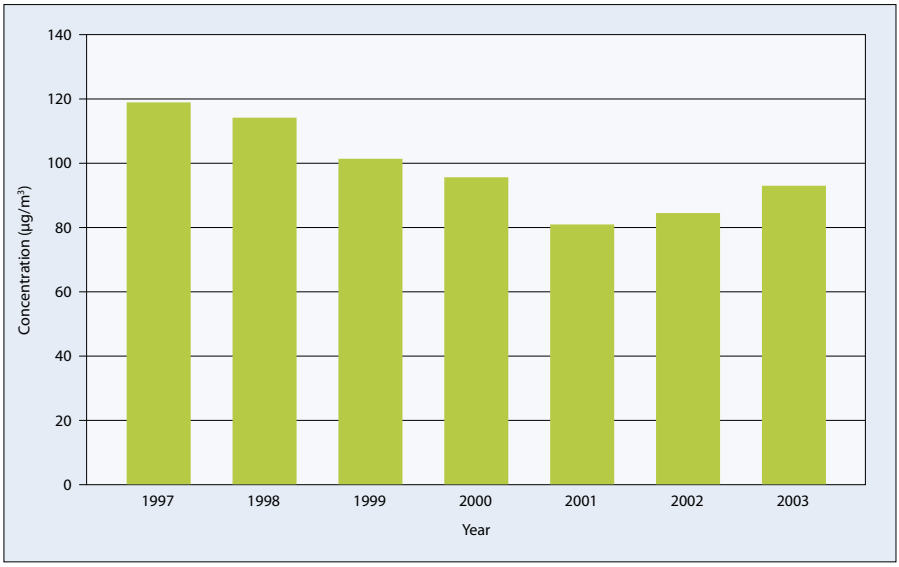
Africa

In Africa, the high rate of urbanization (4–8% per year in a number of cities) that is expected to be sustained for the next decade, combined with low-income solutions to daily commuting, has resulted in a rapid increase in pollutants emitted by motor vehicles. Low incomes have resulted in the importing of older used vehicles in recent years, the use of cheap two-wheeled vehicles and cheap fuel, and the postponement of vehicle maintenance.

In the greater Cairo area, there has been no statistically significant downward trend in sulfur dioxide concentrations since measurements started in 1999, even though levels fell between 1999 and 2001.

In South Africa, ambient levels of sulfur dioxide, nitrogen dioxide and ozone do not show an upward trend. Owing to the lack of monitoring information, however, it is difficult to be specific about numbers and impacts.

Fig. 15. Mean PM_{10} concentrations (April–September) at measurement stations in Santiago, Chile, 1997–2003



Source: Ulriksen & Merino *(20)*.

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3. Human exposure to air pollution

Nicole Janssen, Sumi Mehta

Summary

The concept of exposure is important, both from the point of view of assessing the impact of a pollutant on health and from that of risk management, which often focuses (directly or indirectly) on reducing people's exposure.

Exposure to air pollution is largely determined by the concentration of air pollutants in the environments where people spend their time, and the amount of time they spend within them. On a global scale, the bulk of exposure to air pollution is experienced indoors, as most people spend most of their time there. Assessment of "total exposure" can be essential for the evaluation of health effects from air pollution. The concept of total exposure includes the consideration of outdoor and indoor concentrations of pollutants (and how they vary with time) as well as personal exposure to them.

Different methods of exposure assessment have been established that give qualitatively different exposure estimates and differ with respect to precision, cost, feasibility and other factors. Among those methods are the widely used fixed site measurements of ambient air pollutants, modelled estimates of pollutant concentrations and personal measurements of exposure. A special challenge is the elucidation of long-term effects of air pollution exposure on health, which involves careful evaluation of time-dependent changes in pollutant mixes and changing trends in lifestyle, occupation, transport, housing, etc. Furthermore, there are periods of increased human susceptibility to air pollutants, which – ideally – would be periods of assessment. This includes, for example, exposure of women during pregnancy and its effect on low birth weight. Taken as a whole, exposure assessment provides a way to identify sources whose emissions have the greatest potential to affect the health of the general population as well as of susceptible subgroups.

To reduce the health effects of air pollution, source abatement is certainly the long-term goal. Nevertheless, reducing exposure can serve as a cost-effective way of lessening the health effects. For example, minimizing exposures could involve changes in planning, such as traffic zoning or the siting of polluting industries. It could also entail making changes, such as ▶

- improved ventilation in key microenvironments, and informing/educating susceptible populations in particular on ways to reduce their exposure (for example by staying indoors on days with high outdoor air pollution).

Exposure is a more direct environmental health risk indicator than ambient air measurements, because all environment-related health effects are triggered through exposure. That means that today's burden of disease associated with air pollution is a function of exposures that have occurred (often over many years) in the past. Policy interventions can be targeted to reduce current exposures and the potential for health events in the future.

Definition and concept of exposure

Human exposure can be defined as "the event when a person comes into contact with a pollutant of a certain concentration during a certain period of time" *(1)*. Conceptually, this occurs along the "environmental pathway" between concentration and dose, as follows:

Source → Emissions → Concentrations → Exposure → Dose → Health effects

"Exposure" should be distinguished from "concentration", which is a quantitative expression of the amount of pollutant within a given environmental medium. High air pollution concentrations do not necessarily result in high exposures. For example, while air pollution concentrations may be very high near an emitting industrial facility, high exposures will occur only if people spend time near the facility. Exposure should also be differentiated from "dose", which refers to the amount of pollution that actually crosses one of the body boundaries. The dose will be defined by the characteristics of exposure (as defined above) as well as a wide range of factors specific to the pollutant (e.g. its solubility or pattern of deposition in the lung) and by physiological factors such as the person's level of activity, skin condition, etc.

Most research on the health effects of air pollution has focused on respiratory and cardiovascular effects occurring following inhalation. It should be noted, however, that exposure refers to contact with *any* part of the human body and does not refer to inhalation alone. Other health-damaging routes of exposure to air pollution include dermal absorption and ocular exposure. For example, acute exposure to airborne pollutants can result in eye or skin irritation.

Assessment of exposure to air pollution is the study of how people experience such exposure. Exposure assessment is thus an integral part of air quality management and health impact assessment. It requires exposure estimates that are accurate, precise and biologically relevant, for the critical exposure period, and that quantify the range of exposure levels within the population under study.

Where does human exposure occur?

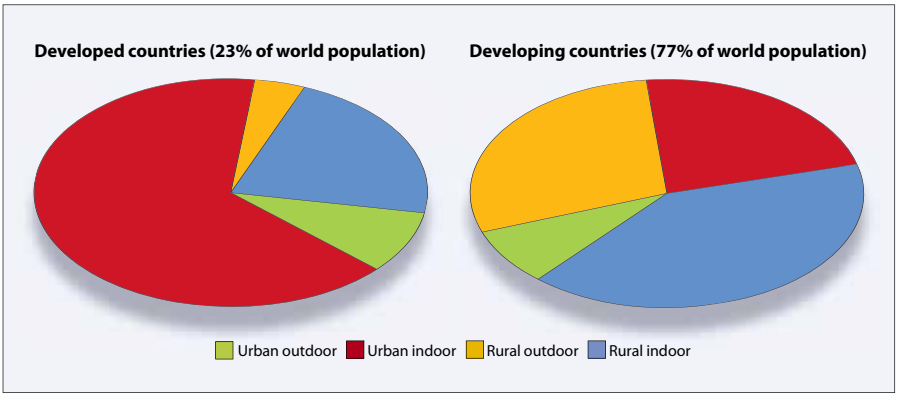
By definition, human exposure occurs where people spend their time. Air pollution levels can show substantial spatial and temporal variation, and people encounter different concentrations as they move from place to place throughout the day. Human exposure is determined by the amount of air pollution in the environments where people spend their time and by the amount of time they spend in them. The environments where people stay are often referred to as "microenvironments" Technically, a microenvironment is defined as a three-dimensional space where the pollutant level at some specified time is uniform or has constant statistical properties. In practice, however, microenvironments are often taken to be a few selected spaces that are considered to make the greatest contribution to total exposure.

The world can be roughly divided into eight microenvironments on the basis of the following three classification schemes.

- ***Indoor versus outdoor.*** People everywhere spend the majority of their time indoors.
- ***Developed versus developing.*** Over 80% of the world's population lives in developing countries *(2)*.
- ***Urban versus rural.*** Urbanization is occurring rapidly, with nearly half of the world's population living in urban areas *(2)*. While over three quarters of the population in developed countries live in urban areas, around 60% of the people in developing countries continue to live in rural areas *(2)*. In the light of these facts, it is clear that the microenvironment with the greatest contribution to global person-time is the rural indoor environment (Fig. 1).

Not surprisingly, then, on a global scale, a large proportion of people's exposure to air pollution also occurs indoors. While indoors, people can be exposed to pollution from indoor sources (see Chapter 9) and from outdoor sources that

Fig. 1. Division of world person-hours into eight microenvironments



Source: K. Smith, personal communication, 2002.

penetrate from outdoors into the indoor environment. While outdoors, people are exposed to pollution from outdoor sources and, in some situations, to pollution from indoor sources as well (see Chapter 9).

Total exposure and time–activity patterns

Most of the studies assessing the health effects of air pollution have used ambient air quality as a proxy for exposure to air pollution, as it is relatively simple and convenient to measure. Air quality guidelines often focus primarily on ambient (outdoor) air pollution *(3)*. Consequently, it is not surprising that major efforts to improve air quality have focused on outdoor sources, such as industrial and energy-producing processes and motor vehicles.

In reality, however, not all aspects of human exposure to air pollution can be captured by air quality monitors. Refining measures of exposure involves taking into account proximity to the source, the amount of time spent exposed, and multiple microenvironments. Total personal exposure refers to the total exposure people experience in all the microenvironments where they spend their time. If the total exposure is dominated by pollution in one microenvironment (e.g. ambient air), controlling the pollutant in this microenvironment assures control of total exposure as well. In many other cases, however, total exposure results from a combination of sources and exposures specific to various microenvironments *(4)*.

Information on people's time–activity patterns, based on detailed time–activity diaries, is often used in conjunction with information on air concentrations in the microenvironments where people spend their time, in order to generate detailed exposure profiles. The most important microenvironments for air pollution exposure are those where people spend the majority of their time, as well as those likely to contain the highest concentrations of air pollutants. These include the home, places of work, schools and traffic corridors. Information on time–activity patterns may be used to estimate total exposure, and also to determine appropriate ways to reduce exposure. Depending on the nature of the pollutant sources, a large proportion of daily exposure may occur in only a few hours. In other cases, exposures are relatively well-distributed throughout the day. In addition, time–activity patterns can provide information on potential peak exposures in specific locations.

The relative importance of short peak exposures as opposed to long exposures to low concentrations depends on the pollutant and the health effect under consideration. Exposure assessment should therefore take into account the most appropriate time average. For example, if one were looking at a heavy metal such as lead, one might simply calculate a long-term average by adding the total personal exposure averaged over each microenvironment. If, on the other hand, one were assessing exposures to sulfur dioxide, the appropriate time average may be of the order of minutes.

People can be exposed to elevated concentrations of certain pollutants while in traffic. High levels of exposure among commuters have been demonstrated in studies conducted all over the world *(5–7)*, although the absolute levels of exposure vary by mode of transportation, by region and by component. Exposures to primary air pollutants (carbon monoxide, benzene, nitric oxide and black smoke) are especially high. For example, in a study of taxi drivers in Paris, the average nitric oxide concentration in the taxi was more than 11 times higher than at a city background measuring site, whereas the level of nitrogen dioxide was only twice as high. Black smoke concentrations (8-hour average) in taxis were on average almost four times higher than those at a city background site *(8)*. In general, cyclists and pedestrians tend to be somewhat less exposed than people in buses and cars *(5)*, although this difference can be offset by longer journey times. In addition, increased breathing rates while bicycling and walking may mean that larger volumes of pollutants are inhaled. A study in Amsterdam showed that carbon monoxide and benzene exposures were over twice as high for car drivers as for cyclists. Nitrogen dioxide exposures showed a similar pattern. Cyclists, however, breathed on average more than twice as much air as car drivers. As a result, car drivers inhaled only marginally higher amounts of carbon monoxide and benzene, whereas the amount of nitrogen dioxide inhaled was in fact significantly higher for cyclists *(9)*.

Exposure to outdoor air pollution is also influenced by the time spent outdoors, and is most important for people or populations who spend a substantial amount of time outdoors. When people spend only limited time outdoors, however, the direct contribution of outdoor air to personal exposure will generally be low, and most of the exposure to outdoor air pollution is actually encountered indirectly through the effect of outdoor air on indoor air *(10)*. This is particularly the case for non-reactive pollutants that penetrate easily from outdoors to indoors; for these pollutants time spent outdoors will have only a modest effect on total personal exposure. For some reactive pollutants such as ozone, or pollutants like coarse PM that penetrate poorly from outdoors to indoors for mechanical reasons, the indoor concentrations are much lower than those outdoors; for such pollutants the time spent outdoors can be a very important determining factor for exposure *(11)*.

When people spend only a limited amount of time in traffic or outdoors (~1–2 hours per day), the relative contribution to long-term average personal exposure is relatively low. In a study in Amsterdam and Helsinki, for example, 24-hour average personal exposures to black smoke increased by about 10% per hour spent in traffic and about 10% per hour spent outdoors. Some of the soil-related elements (iron, calcium, silica) also showed significant associations with time spent in traffic, suggesting a contribution from resuspended road dust *(12)*. The contribution is obviously greater for populations that spend longer periods in vehicles or outdoors, especially when close to hot spots such as busy roads. In addition,

a relatively modest contribution to long-term average exposure should not be interpreted as implying that this kind of contribution is not important, as little is known about the health effects of short-term increases in exposure. For example, Peters et al. *(13)* found that the time spent in traffic was consistently linked with an increase in the risk of myocardial infarction one hour later. It is unclear, however, to what extent traffic-related factors other than air pollution contributed to the elevated risk observed in this study.

The influence of location on the relationship between sources and exposures

The potential for a pollutant to affect human health is determined as much by a pollutant's exposure effectiveness as by its relative toxicity *(14)*. Exposures are heavily influenced by the location of sources with respect to potentially exposed populations. "Exposure effectiveness" can be defined as the fraction of pollutant that actually enters a person's breathing zone. In other words, this is the amount of material that could actually be inhaled, ingested or absorbed by an individual. A number of terms have been used interchangeably to refer to this concept, including intake fraction, potential intake, and fate factor *(15)*. The basic concept remains the same, however: it is not only the quantity or relative toxicity of a source that must be considered, but also the total amount likely to reach people.

Depending on their proximity to people, different sources of the same pollutant can result in vastly different amounts of exposures. Exposure efficiency is greatest close to the source. For example, estimates suggest that although benzene emissions from household cigarette smoke are only a minute fraction of the emissions from vehicles, cigarettes can have an intake fraction up to a few hundred times greater than outdoor emissions *(15)*. At the same time, benzene from vehicles may result in exposure of a much larger proportion of the population, albeit at much lower levels. While the contribution of cigarettes to total benzene emissions is close to negligible, their contribution to personal exposure is substantially greater.

Methods of exposure assessment

The choice of exposure assessment method should be driven by the questions being asked. In some cases, exposure assessment is used to inform public health research, i.e. as an integral part of epidemiological studies. In other cases, exposure assessment is an important input to policy and/or planning decisions, such as when designing effective intervention programmes and control strategies, or evaluating compliance with regulatory standards.

Depending on the purpose of the exposure assessment, several key factors influencing exposure should be kept in mind, including geographical determinants of exposure and temporal trends in exposure. Sensitive subpopulations who may be particularly susceptible to higher exposures should be identified. Other

practical factors, including cost, accuracy and the feasibility of attaining necessary input parameters, must also be taken into account.

Human exposure to air pollution can be characterized in different ways. While one would ideally like to know exactly how much air pollution each individual comes into contact with, several methods (with varying levels of precision and on different geographical scales) can be used to estimate exposure to air pollution. For a summary of exposure modelling approaches, see Table 1. Models based on different types of data will give qualitatively different exposure estimates.

In general, as the precision of exposure measures increases (from the top to the bottom of Table 1), the availability of pre-existing or routinely collected data decreases and the cost of collecting original data increases.

Qualitative and/or secondary data sources

Qualitative and/or secondary data sources, such as data on traffic characteristics, the distance of the home from a busy street, traffic intensity on the street of residence, energy consumption and information on indoor sources, can be used to indicate potential exposure. These exposure estimates are often obtained from the subjects themselves by means of questionnaires, although with the growing availability of GIS databases some types of information can increasingly be obtained from objective data sources. The underlying quantitative relationship between these qualitative exposure estimates and actual exposures can vary substantially between studies. For example, a study in Jimma, Ethiopia found that living in close proximity to busy roads was associated with increased risk of wheeze *(16)*, which is in line with several studies conducted in industrialized parts of the world. Median traffic density, however, was only 653 vehicles per 12 daytime hours, with a maximum of only 2640, which would not be regarded as a busy road in cities in the developed world. It is conceivable, however, that 600 vehicles in Jimma count for a lot more, in terms of pollutant emissions, than 600 vehicles in developed countries *(17)*. Differences in the chemical composition of fuels, meteorological conditions, percentages of heavy polluters, vehicle maintenance and the quality of and control measures for vehicles make it difficult to generalize findings across studies *(7)*.

Measured estimates from fixed sites

These provide periodic, accurate concentration information at the point of monitoring, but do not necessarily reflect exposures of individuals. These estimates assume that all individuals in a specific area have the same exposure, and ignore spatial variability within an area as well as possible differences among individuals in outdoor living. Nevertheless, since it generally does reflect daily changes in ambient levels, this measure has often been used as the indicator of exposure in many studies of the health effects of short-term exposures to ambient air pollution. While ambient monitors are able to capture daily temporal or spatial

Table 1. modelling approaches to exposure assessment

Measure	Examples of exposure estimate generated	Sample data inputs to the model
Qualitative estimates	Proximity to traffic	• Distance to busy streets • Traffic composition and flow • Energy consumption
Source-specific estimates	Source-specific estimates of exposure	• Source receptor models • Dispersion models
Ambient concentrations at fixed site (measured)	City-specific estimates of exposure Longitudinal estimates of exposure	• Average daily concentrations of air pollution, weather, meteorological data
Ambient concentrations (modelled)	Spatially resolved estimates of exposure	• Geographical information systems (GIS) incorporating emissions data, dispersion models and/or traffic patterns
Indirect personal measurement	Population estimates of exposure (representing the range of exposures experienced by individuals within a population) Individual estimates of exposure Individual estimates of long-term exposure	• Probabilistic models incorporating variability in exposure data • Time-activity patterns in conjunction with location-specific estimates (modelled or microenvironmental) • Historical air pollution data in conjunction with individual activity profiles, or information on factors influencing individual exposure
Direct personal measurement	Individual estimates of exposure	• Continuous measurement using personal monitors • Time-averaged measurements • Intermittent measurements
Direct personal dose estimation (biomarkers)	Individual measurements of biomarkers	• Blood lead levels • Carboxyhaemoglobin in blood as a marker for carbon monoxide

variations in indoor concentrations or personal exposure in developed countries *(10)* and urban areas of developing countries *(18)*, they may not reflect total exposure when there are strong local or indoor sources. In particular, in areas with large sources of indoor pollution, such as where people continue to cook with solid fuels, indoor concentrations may be larger and poorly correlated with concentrations from ambient monitors *(19)*.

Modelled estimates of air concentrations

More expensive, but not necessarily more accurate, are modelled estimates of air concentrations based on data from multiple sources. Outdoor exposure estimates are often based on available ambient air quality data, emission profiles and dispersion models. These are intended to provide a wider spatial distribution of exposures, and are being increasingly used in health studies. Depending on the major sources present, indoor exposure estimates can be based on indoor and outdoor concentrations, housing characteristics and pollutant dispersion (transformation, penetration, decay rate) characteristics.

A recent development is the use of geographical information systems (GIS) to estimate individual exposure to air pollution in large-scale epidemiological studies *(20)*. In this approach, information on specific qualitative and/or quantitative surrogates is collected for all individuals. Subsequently, the knowledge of the quantitative relation between those surrogates and exposure is used to model individual exposures.

Even more precise, but also more expensive, are exposure assessments that involve the direct measurement of people's exposures through personal sampling. Measurements taken in the subject's breathing zone, using personal monitors, are often considered the most accurate estimate of a person's "true" exposure. In practice, however, it is generally not possible to actually measure such personal exposure for large numbers of people. This is because a suitable measuring method is not always available, or that available measuring methods are usually very labour-intensive, expensive or intrusive for the people concerned.

Personal exposure studies in smaller samples of subjects, in particular population-based samples, however, can provide invaluable information for calibrating models, understanding relationships with ambient concentrations in time and space, and identifying key determinants of personal exposure that might be the subject of policy interventions.

In addition to direct measurement, personal exposure can also be determined indirectly. This involves measuring the concentration of air pollutants in the spaces (microenvironments) where the subjects are staying, as well as measuring the amount of time spent in these spaces. In practice, this approach involves measurements or modelling of concentrations in a few selected microenvironments that are considered to have a major contribution to personal exposure. In view of the large amount of information required, this method is often not suitable for large-scale use.

Finally, for some pollutants such as lead and carbon monoxide, exposures and resulting doses can be estimated from biomarkers. Owing to the multiple sources of airborne pollution in most human settlements, however, biomarkers generally lack the specificity to inform regulatory decisions.

The purpose of the assessment should determine the method used. For example, in health studies to evaluate the effect of short-term changes in air pollution, such as time series studies, exposure estimates need to demonstrate variations in time on a daily or near-daily basis. Exposure variables that are (more-or-less) constant in time, such as traffic characteristics, would therefore not be appropriate for this type of study. Although they are generally considered a more accurate assessment of exposure, depending on the study methodology used, personal measurements do not necessarily provide more valid data than stationary outdoor measurements. For example, a personal sample in a study investigating the effects from outdoor combustion pollutants is often influenced by sources other than outdoor sources. Thus a measurement of total personal exposure does

not necessarily provide the most relevant information. Also, a personal measurement of a single air pollution component may not adequately reflect exposure to complicated mixtures of pollutants, especially in the absence of a strong specific marker. In this case, a quantitative or qualitative surrogate could provide a more valid exposure estimate.

Where individual exposure estimates are needed in health effects studies, from an air quality management perspective information on population exposure *distribution* is more relevant. In terms of data needs, costs and model complexity, population exposure distributions can most efficiently be estimated using probabilistic modelling. The advantage of probabilistic models over statistical, empirical models (e.g. regression and factor analysis) or physical, deterministic models (e.g. dispersion and mass balance models) is that limitations of unavailable data for specific individuals are overcome by using the probability distributions of the input values instead. Input distributions incorporate the variability in the exposure factor data across as many individuals and conditions as data are available. In addition to population averages, the predicted exposure distribution provides the range in exposures for the general population or subpopulation of interest, and the likelihood of exposures above a particular level *(21,22)*.

Probabilistic modelling can be used to support policy-making and policy evaluation by evaluating air pollution exposures in different (hypothetical) scenarios, population groups and locations *(21)*. For example, Hänninen et al. *(23)* developed a probabilistic simulation model to evaluate the exposure reduction potential of a mechanical supply and ventilation system with air supply filtration that was becoming standard for occupational buildings in Helsinki in 1990 and increasingly common in homes. The model was used to assess population personal exposures to $PM_{2.5}$ in Helsinki's working-age population. It was estimated that if the non-ETS-exposed working-age population all lived and worked in buildings with similar filtration efficiencies, their exposure to $PM_{2.5}$ could be reduced by 27%.

Seasonal trends

Seasonal patterns are extremely location-specific, and may vary substantially from year to year. The impact of seasonal patterns on the relationship between indoor and outdoor concentrations needs to be carefully evaluated. In some places, extremes of temperature are often addressed by controlling indoor temperatures in ways that limit ventilation (such as with increased use of air conditioning or heating). In other places, however, increases in temperature may increase the air exchange rate of housing, owing to resulting changes in physical exchange processes as well as changes in human activity (such as opening windows and doors more frequently in warmer weather). The impact of these changes on human exposure will depend on the location of pollution sources (indoors or outdoors) as well as any changes in activity patterns attributable to the season.

Assessing long-term exposure to air pollution

An accurate assessment of long-term exposure to air pollution is necessary when studying its chronic effects. Whether done retrospectively or prospectively, this involves careful attention to trends in sources of air pollution as well as trends in lifestyle.

Assembling data on trends in air quality and lifestyles over long periods is not easy, since retrospective data may vary widely in composition and quality. It is not surprising, then, that retrospective studies of the effects of long-term/chronic exposure to air pollution face major challenges owing to the limited availability of key data. Estimating long-term exposures is likely to involve the assessment of trends in local sources, air pollution levels and distributions, particle composition, monitoring methods, migration and lifestyle. The harmonization of qualitatively different indicators of pollution alone can present a major challenge. For example, historical data on PM may include measures of black smoke, total suspended particulates, respirable particulates, PM_{10}, $PM_{2.5}$ and even ultrafine particulates. As societies continue to grow and evolve, the nature of the sources contributing to the same PM fraction may change and/or the composition of the pollutant mixture may change, and air pollution levels change as a result. The composition of air pollutants, as well as their spatial distribution, is also likely to change.

Past exposures will be influenced by the movement of study participants. Even in the same location, lifestyle characteristics related to exposure, including occupation, transport and housing, also change over time. This is particularly true with the rapid increase in urban lifestyles.

Nevertheless, some studies have attempted to assess historical long-term residential concentrations as a measure of long-term exposures. For example, in a study of lung cancer in Stockholm, Bellander et al. *(24)* used reconstructed emission data, dispersion models and linear intrapolation and extrapolation to estimate annual average nitrogen dioxide and sulfur dioxide concentrations for the years 1955–1990. These annual air pollution estimates were next linked to annual residence coordinates using GIS. Tager et al. *(25)* assigned residence-based ambient ozone exposure values by interpolation of ambient ozone monitoring data to residential locations. Estimated lifetime exposure was based on average ozone levels between 10:00 and 18:00 and hours of exposure to ozone concentrations greater than 60 ppb. In addition, an "effective" lifetime exposure to ozone was calculated, based on a weighted average of estimated time spent in different ambient ozone environments as determined by different combinations of activity data. Estimated effects on pulmonary function were unaffected by the method used to estimate lifetime exposure and gave effect estimates that were nearly identical.

Critical time windows

When using exposure assessment to inform health studies, it is extremely important to ensure that appropriate time windows, reflecting biologically plausible periods of susceptibility, are assessed. The "ideal" time window or windows is often unknown. Thus, particularly when assessing chronic, childhood or developmental effects, it is important to reconstruct as much of a subject's lifetime exposure as possible. In fact, the effects on children's health of exposure during pregnancy, as well as exposure of the parents prior to conception, are becoming increasingly important topics in research into the effects on health of air pollution. For example, in a systematic review of studies on the effects of ambient air pollution and prenatal and early childhood effects, Lacasana et al. *(26)* identified 12 studies evaluating the association between exposure to outdoor air pollution and low birth weight. In 10 of these studies, low birth weight was significantly associated with air pollution levels. However, there was no consistency as to which trimester of pregnancy was most relevant or the specific pollutant that might represent a higher risk. In another review on the topic, Sram et al. *(27)* also stress the need for further studies to clarify the most vulnerable period of pregnancy and the role of different pollutants.

Relationship between personal exposure, indoor concentration and outdoor concentration

As mentioned above, estimates of exposure to air pollution are usually based on measurements of the ambient concentrations at a fixed site. The extent to which ambient air quality estimates from monitoring networks or models correspond to personal exposure in the population is an important factor to be considered in setting standards for ambient air quality. This will depend on the pollutant in question as well as on a number of local characteristics, including lifestyle, climatic conditions, the spatial distribution of pollution sources and local determinants of pollutant dispersion. Another important issue is how much of total human exposure is due to ambient, outdoor sources as opposed to indoor sources. This may vary substantially from one country to another. For example, indoor air pollution levels might be quite substantial in countries in which fossil and/or biomass fuels are used in homes.

Key factors determining the relationship between indoor and outdoor concentrations

As many people spend most of the day indoors, the relationship between outdoor and indoor air is obviously important and is determined by:

- spatial variation in ambient air concentrations;
- penetration into the indoor environment of outdoor-generated air pollutants; and
- indoor sources of the air pollutants under consideration.

Spatial variation in ambient air concentrations

Spatial variation determines to what extent ambient concentrations measured at a single fixed site reflect the outdoor concentrations at other sites in the area. An important factor for the spatial variation of a primary air pollutant is the geographical distribution and type of the emission sources (e.g. line source, point source). After the emission takes place, inert pollutants such as carbon monoxide simply disperse and a concentration gradient with increasing distance to the source develops. For chemically reactive pollutants, such as nitric oxide, a steeper concentration gradient than for inert pollutants develops. In contrast, the formation of secondary pollutants is a large-scale phenomenon and these pollutants have quite uniform spatial distributions. Furthermore, diffusion and transport of pollutants are determined by atmospheric conditions such as wind speed and solar radiation. The time-scale of the small-scale spatial variation may also be important. The size of short-term spatial fluctuations is different from spatial fluctuations in annual means *(28)*.

For PM, the spatial variability depends on the size fraction. For fine particles, the spatial variability is generally small, whereas ultrafine and coarse particles have a much stronger spatial variability *(29,30)*. Even for fine particles, however, the spatial variation can be significant for specific components such as elemental carbon (e.g. diesel soot) *(31)*. Nitrogen dioxide concentrations exhibit quite strong spatial variability owing to local sources such as cars. While the spatial variability of ozone is rather low across larger areas, within city gradients it can be pronounced owing to the reaction of ozone with traffic and other combustion emissions of nitrogen oxides *(3)*.

Penetration indoors of outdoor-generated air pollutants

The amount of air pollution penetrating from outdoors to indoors depends on the penetration coefficient, the ventilation rate and the decay rate *(32)*. Particles in the ambient air penetrate to the indoor air, although some filtering takes place. The smallest particles penetrate almost completely from outside to inside. Ozone is a highly reactive component that reacts quickly with surfaces when penetrating indoors, which is why ozone levels indoors are generally much lower than those measured outdoors. Ozone concentrations, however, are generally high during hot and sunny weather, precisely the conditions under which people open their windows and doors and spend more time outdoors. Nitrogen dioxide is also reactive, albeit less than ozone. In the absence of sources in the indoor air, nitrogen dioxide and sulfur dioxide concentrations indoors will be lower than those outside.

Household ventilation is a function of both climate and development. Ideally, such ventilation is appropriate to the surrounding environment, with reduced ventilation rates in colder climates/seasons and increased rates in more temperate climates/seasons. Ventilation tends to be better controlled with increased

economic development. For example, many eastern European countries use solid fuels for heating, but with much more sophisticated solid fuel energy technologies than are available in developing countries. Thus, residents can cook and/or heat with solid fuels without creating large indoor sources of exposure. In contrast, people living in poorer households in developing countries, particularly those living in less permanent structures, generally have much less precise control over their household ventilation rates. Their households are likely to be very open in hot weather and as tightly sealed as possible in the winter. Seasonal variations in household ventilation are therefore likely to be substantial.

The flux of air pollutants penetrating the house increases with the ventilation rate. The ventilation rate of houses depends on the building characteristics, weather conditions and the (ventilation) behaviour of the occupants. In very well-insulated houses, the ventilation rate is low and thus the amount of air pollution from outside will be lower. In very well-insulated houses, however, pollutants produced indoors accumulate more and moisture problems may occur. The ventilation rate will be higher when it is windier outside, when the temperature difference between indoor and outdoor air is higher, and when the windows are open for a longer period. In a study in Baltimore *(33)*, for example, personal exposure to fine PM of outdoor origin in the summer was found to be almost twice as high for people who had had their windows open for more than 72% of the time compared with those who had hardly opened their windows (<4%). In another study in the United States *(34)*, the rate at which the air was refreshed in houses with air conditioning was some six times lower than in houses without air conditioning. The concentration of sulfate, a component of fine PM for which there are hardly any indoor sources, was almost twice as high in houses without air conditioning. The reducing effect of air conditioning also applies to exposure in vehicles. For example, in a study among commuters in Hong Kong, China *(35)*, the average $PM_{2.5}$ and PM_{10} concentrations in air-conditioned buses were almost half those in non-air-conditioned buses.

The penetration factor from outdoor to indoor air has been shown to vary for the different particle size fractions, with the highest values for accumulation (fine) particles and lower ratios for coarse and ultrafine particles. For a typical home with an air exchange rate of 0.75 air changes per hour and no indoor sources, it has been estimated that the concentration of fine PM indoors will be on average about 65% of the outdoor concentration. For nitrogen dioxide the figure is approximately 40–50% *(28)*. For ozone and sulfur dioxide this ratio is generally much lower.

Indoor sources

Indoor sources (see Chapter 9) can significantly contribute to a person's total exposure. The relevance of indoor sources in health impact assessment depends on whether one is interested in the health effects of total human exposure (including

both exposures from outdoor origin and indoor sources) or only in that part of the exposure that is from outdoor origin. For pollutants such as benzene (where no constituent differences exist and the toxicity of outdoor and indoor exposure is the same) optimal exposure-based air quality management would in some cities point to ambient sources and in others to indoor sources (even consumer products), depending on which sources dominate the personal exposure *(4)*. For PM, however, the composition of particles of outdoor origin can be very different from that of particles from indoor sources. Methodological investigations have therefore pointed out that ambient and non-ambient exposures need to be considered as two separate classes of pollutant *(36,37)*. Ebelt and colleagues *(38)* developed separate estimates of exposure to ambient and non-ambient particles based on time–activity data and the use of particle sulfate measurements as a tracer for indoor infiltration of ambient particles, and evaluated their relative effect on cardiopulmonary health. Although total and non-ambient particle exposures were not associated with any of the health outcomes, ambient exposures were associated with reduced lung function, lower systolic blood pressure, increased heart rate and increased supraventricular ectopic heartbeats. These results obviously do not imply that non-ambient exposures cannot have health effects of their own in other settings.

Since people spend most of their time indoors, most of the exposure to pollution of outdoor origin takes place indoors, where exposure can be modified by the building and its equipment (e.g. air conditioning). If one is primarily interested in pollutants of outdoor origin, indoor concentrations are of interest only in so far as they reflect or do not reflect outdoor concentrations and sources. This concept has been most advanced for particle exposure, but can apply to other components with significant indoor sources as well, provided that it is not the pollutant per se that is causing the health effects. From a policy perspective, however, interventions based on reducing specific indicator pollutants that are not necessarily directly related to health may not result in the most effective strategies. For example, it remains unclear whether the observed association between nitrogen dioxide and health is due to the nitrogen dioxide itself or whether nitrogen dioxide is an indicator of other correlated pollutants, such as ultrafine particles and traffic-related pollution in general *(3)*.

Reduction of pollution generated indoors

One of the most practical ways of reducing exposure to indoor sources of air pollution has been the outdoor dissemination of indoor sources of pollution. For example, while chimneys do not change the quantity of smoke emitted, they reduce indoor exposures to smoke substantially.

Indoor sources can make a substantial contribution to outdoor concentrations in places where there are large, widespread sources of indoor air pollution. For example, the infamous London Fog was caused essentially by indoor use of coal for

space heating. The amount of air pollution penetrating from indoors to outdoors depends on household characteristics, weather conditions and the behaviour of the residents. In communities where large proportions of the population use solid fuels for cooking and heating, indoor emissions make considerable contributions to local or neighbourhood outdoor air pollution levels *(39)*. Indoor sources can make a substantial contribution to outdoor concentrations, even in the absence of chimneys and/or flues. Indeed, in many areas of developing countries, especially rural areas and areas with dense clusters of low-income houses, indoor air pollution can be one of the largest contributors to outdoor air concentrations.

Overall strength of the relationship between personal (or indoor) and outdoor concentrations

The question as to what extent ambient air concentrations accurately reflect personal exposure depends on the type of study or health effect one is interested in. For *acute effects*, one would like to know whether the exposure of individual citizens followed from day to day varies with the respective day-to-day variation in ambient air pollution concentrations. Although this association has been shown to vary from person to person, on a population level this correlation is considered to be sufficiently high to justify the use of outdoor concentrations as a measure of exposure in this type of study. This is especially the case for components that penetrate easily from outdoors to indoors and have few indoor sources *(10,40)*. For pollutants with low effective penetration from outdoor to indoor environments, such as ozone, significant correlations have been found only for outdoor workers or during warm weather *(41,42)*.

Most of the studies that document a strong day-to-day association between personal and ambient PM concentrations have been conducted among people with little exposure to non-ambient particles (such as nonsmoking elderly people). A study among healthy adults, however, reported very low associations *(43)*. Results from the EXPOLIS study also suggest that outdoor monitors are less effective in estimating exposures in active, working adults than in those with a low activity level who stay at home *(44)*. Outdoor levels of sulfur, however, were highly correlated with personal or indoor sulfur exposures, suggesting that outdoor concentrations accurately reflect personal exposures to fine particles of outdoor origin for these populations also *(45)*.

For *long-term effects*, the question depends on the geographical scale of interest. When comparing the occurrence of disease in cities with different average concentrations of ambient air pollution, the correlation between average outdoor concentrations and city-average personal exposures is relevant. For assessments on a smaller local scale (for example the long-term effects of traffic-related air pollution), however, one needs to know whether the exposures of different individuals across an area reflect the respective outdoor air concentration differences near where they live (or work). Since measuring personal exposures over longer

periods of time involves major logistical complications, the relationship between long-term ambient air pollution concentrations and long-term average personal exposures is difficult to assess. Studies that have compared average personal exposures of people from different countries or communities, with different average outdoor air pollution concentrations, however, generally show that those in the countries/communities with the highest ambient concentrations had the highest personal exposures and vice versa *(28,46)*. Central-site long-term average outdoor concentrations should therefore reflect with sufficient accuracy the differences in average personal exposures between communities, again especially for homogeneously distributed air pollutants (such as fine particles) that penetrate well from outdoor to indoor environments. In a study in seven American cities, for example, indoor particle concentrations were about twice as high as outdoor concentrations. The effect of indoor sources, however, was found to be similar in all cities, implying that differences in indoor concentrations between the cities are mainly caused by differences in outdoor concentrations *(47)*. For air pollutants with high spatial variability, such as traffic-related pollutants, the correlation between personal and central-site outdoor concentrations is lower, but measurements or estimates of outdoor concentrations just outside the home are more strongly related to personal exposures. Individual activity patterns (e.g. time spent in traffic), however, can significantly influence personal exposures independently of residential outdoor concentrations.

Much of the research on the relationship between personal or indoor and outdoor air has been conducted in Europe and North America. Less is known about these relationships in other parts of the world. Given the considerable differences in sources of pollution, location of pollution sources with respect to populations, habitation patterns and building characteristics, the relationship could vary substantially across regions. A study conducted in Bangkok, however, also suggested that ambient monitors were able to capture the daily variation in indoor PM_{10} levels *(18)*. A personal exposure study of children living in Santiago de Chile also showed strong cross-sectional associations between personal, indoor and outdoor $PM_{2.5}$ levels. Correlations for nitrogen dioxide were weaker, probably owing to the presence of gas cooking stoves in all homes *(48)*. A study in four Mexican cities, however, did show that the best predictors of personal nitrogen dioxide exposure were outdoor levels and time spent outdoors *(49)*. In the absence of strong indoor sources, personal–outdoor correlations could actually be stronger in relatively polluted locations, since elevated ambient levels may obscure the influence of non-ambient sources and increase the relative contribution of outdoor particles to personal exposure *(48)*.

Population characteristics

While exposure assessment can be used to estimate exposures experienced by the "average" individual, it is often used to address populations most likely to be at

risk. This includes populations likely to experience the highest exposures, as well as those most susceptible to these exposures. Host factors, such as activity, lifestyle, behaviour and susceptibility, must be taken into consideration. Susceptible populations include young children, the elderly and the immunocompromised. Certain occupations, such as roadside vending, would be likely to result in higher than average exposure to traffic pollution.

Socioeconomic status may also affect the potential for higher exposures, as well as increased susceptibility. In California, for example, certain ethnic groups have consistently borne a disproportionate burden in the location of polluting sources, including Toxics Release Inventory facilities *(50)*. Racial and economic characteristics have also been shown to differ by proximity to roads *(51)*. In developing countries with large localized sources such as household solid fuel use and refuse burning, and with makeshift housing often located near dense traffic corridors, intra-urban gradients in exposure are likely to be even more pronounced. For a more detailed discussion, see Chapter 6.

Impact of exposure measurement error

There is no single standard for assessing exposure to air pollution. Exposure estimates should thus be regarded as approximations of the "true" exposure of the people being studied. As measurement error can vary widely from one exposure indicator to the next, measurement error and its implications for the interpretation of health studies need to be carefully considered on a case-by-case basis. For example, self-reported and GIS modelled estimates of traffic intensity have been shown to be poorly correlated, with people tending to overestimate their exposures compared to the model *(52)*. Measurement error models for time series studies of air pollution and mortality have also been created *(53)*.

The extent to which such an approximation differs from people's "true" exposure is referred to as "exposure error" for continuous measures and "exposure misclassification" for categorized measures. In general, there are two types of error that should be considered. "Classical" errors are those where the magnitude of error would be the same at all exposure levels, i.e. errors are independent of the "true" exposure. This may be the case, for example, when there are differences between measured and "true" pollution levels arising from instrument error. This would result in a bias towards the null.

In air pollution research, a single exposure level is often assigned to multiple individuals. The difference between the true exposures of individuals, which will vary around this estimated value, is referred to as Berkson error. These errors are independent of the observed value. This type of error causes little or no bias. Random errors in exposure measurements, Berkson or otherwise, reduce the power of a study and make it more difficult to detect an existing association between air pollution and health. Overestimation of the health effect (bias away from the null) is exceptional and usually arises only in rather extreme and unusual cases *(54)*.

Another concern of exposure error is that it may mask the existence of a threshold. In a simulation study, Brauer et al. *(55)* demonstrated that this can indeed occur in cases where exposure estimates are not highly correlated with personal exposures, while exposure indicators that are highly correlated with personal exposures accurately reflect the underlying threshold.

When multiple pollutants are involved, the problem is rather more complex, as it requires information on differences between measured and actual pollution levels for each pollutant as well as differences in correlations across pollutants. Schwartz & Coull *(56)* recently proposed a method that deals with multiple exposures and, under certain conditions, can be resistant to measurement error. To demonstrate the impact of this methodology, Zeka & Schwartz *(57)* applied this method to the data from the National Morbidity, Mortality and Air Pollution Study (NMMAPS) and found a slightly greater effect of PM_{10} than that reported previously by NMMAPS. In addition, an important effect of carbon monoxide was found that had not been observed previously.

In summary, while much of the debate about the existence of a causal link between air pollution and health effects has focused heavily on exposure measurement error *(58)*, approaches to assessing the impact of measurement error on study results do exist. It is therefore important to address carefully factors influencing the impact of measurement error on study results.

Policy implications of exposure assessment

Policy-makers who examine the options affecting air quality management strategies need to take into account the effects of air pollution on public health as well as the benefits and costs of measures to reduce pollution. Evaluation of the effects of policies needs to rely on exposure assessment. If air pollutants have no threshold, exposure reductions at all levels should result in health benefits, at least for some individuals. The most effective way to develop and select effective risk reduction strategies is to attribute exposures and associated risks to microenvironments, activities and emission sources. Exposure models are then used to assess the consequences of alternative exposure scenarios and risk reduction strategies *(4)*.

To optimize interventions aimed at reducing the risk to public health, including investments to control pollution sources, the relative contributions of sources to exposures in major microenvironments should be known and the potential effects on health impact of these exposures should be evaluated. Based on such assessments, control policies and actions to reduce exposure and public health risk may target sources of ambient pollution, sources of pollution in other microenvironments, building characteristics (including ventilation) and other factors that influence personal exposure.

Table 2 lists a number of possibilities for policy action, divided into instruments suitable for outdoor and indoor environments.

Table 2. Possibilities for policy action in relation to indoor and outdoor sources and personal activity

Policy option	Outdoor environment	Indoor environment	Personal activity
Air quality standards and guidelines	++	+	–
Source control and dilution control	++ Traffic control measures Relocation or strategic siting of polluting industries	++ Building codes and ventilation regulations Regulations on building and consumer products Smoking restrictions	+ Car inspections and emission controls Wood stove catalyst requirements
Information/ education	+ Air quality warnings and/or predictions	+ Ventilation, behaviour; smoking, heating, cooking, product use, warning labels	+ General risk communication
Market-driven instruments	+ For example, emissions markets for acid rain precursors in the United States	++ "Eco" labelling of products Bans	+ Tobacco taxes Traffic fuel taxes, car pooling

Note. ++ = strong possibilities for policy action; + = possibilities for policy action; – = policy action not feasible.
Source: World Health Organization *(4)*.

Quantitative evidence on the effectiveness of potentially key exposure reduction strategies is somewhat limited, but some examples can be given. In areas where large proportions of the population continue to cook with solid fuel, improved stoves with chimneys venting to the outside can be used to minimize indoor exposure in the short term, until sustainable forms of cleaner fuels can be attained. Indeed, a review of China's improved rural household stove programme found that improved stoves do result in reduced PM_4 concentrations indoors *(59)*. Janssen et al. *(60)* found that the percentage of homes using air conditioning modified the effect of ambient PM_{10} concentrations on hospital admissions for cardiovascular disease and chronic obstructive pulmonary disease, a lower effect being observed with an increase in the percentage of homes using a centralized air conditioning system.

Reduction of source emissions clearly remains the long-term goal, but where source abatement is slower than ideal owing to economic constraints, appropriate technology or political will it is essential to find other ways of reducing exposure.

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4. Health effects of air pollution: an overview

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Summary

Exposure to air pollution has been associated with a variety of adverse health effects. Most of the recent evidence focuses on respiratory and cardiovascular effects attributed to short- and long-term exposures, as well as on the development of pregnancy-related outcomes. From a public health point of view, it is important to acknowledge that the total impact of air pollution on the population is likely to be dominated by the less severe health effects such as subclinical and symptomatic events. The proportion of the exposed population affected by those outcomes is much larger than that affected by more severe events such as emergency admission to hospital and death. Nevertheless, the severe outcomes (including increased risk of mortality and reduced life expectancy) are most often considered in epidemiological studies and risk analysis, owing usually to the better availability of routinely collected data.

Ailing individuals in the population carry a higher burden of the more severe health effects. For example, death occurs more frequently in those who are already ill, and those with pre-existing medical conditions are more likely to be admitted to hospital or visit an emergency department. Other susceptible subgroups include young children, poorer people and those with low educational attainment. Susceptibility is determined not only by personal characteristics such as age, health status, diet and genetic make-up, but also by environmental factors including exposure characteristics (e.g. time–activity pattern), housing and environmental conditions at the neighbourhood level.

The increased risk of suffering the most common health effects caused by exposure to air pollution is relatively small (a few per cent). Nevertheless, the absolute number of people affected is significant owing to the widespread nature of the exposure and our inability selectively to protect more vulnerable groups from its effects.

Research into the underlying biological mechanisms through which some air pollutants exert their effects on health has focused mainly on inflammatory and oxidative stress-related processes. For other health effects, ▶

- such as adverse pregnancy outcomes, our understanding of biological pathways is currently very limited.

Most evidence linking various human health effects to ambient levels of air pollution stems from epidemiological studies supplemented by toxicological research. In both fields, there are several types of study established, and the study design has to be chosen with respect to the health effect being investigated.

Introduction

There is robust scientific evidence indicating that exposure to air pollutants can affect human health in a variety of ways, ranging from subtle biochemical and physiological changes to severe illness and death. Studies reporting such effects have been carried out since early last century, when marked increases in mortality and morbidity followed short-term episodes of extremely high levels of air pollution *(1–3)*. This and subsequent evidence resulted in the adoption of ambient air quality standards to safeguard the public from the most common and damaging pollutants, especially those derived from the combustion of fossil fuels.

The introduction of cleaner fuels, and the implementation of pollution control technologies that followed, successfully reduced levels of air pollution in several urban areas during the second half of the twentieth century. With levels comparatively lower, air pollution no longer seemed to pose a threat to health. In fact, studies conducted during the 1960s and 1970s suggested that air pollution levels at that time were safe *(4)*. Increasing computational capacities, however, which in turn aided the development and application of more sensitive statistical techniques, later showed the occurrence of health effects at levels lower than those traditionally considered safe. Thus, despite improvements in air quality in many cities of the world, associations between ambient air pollution and mortality were again being reported.

A new generation of studies has since become available, providing more information on the relationship between air pollution and health. Epidemiological studies conducted in many urban areas of the world have uncovered a new series of health end-points associated with exposure to air pollution. In parallel, a better understanding of the underlying biological mechanisms of such effects has evolved.

This chapter provides an introduction to the health effects associated with air pollution, which are more fully discussed in the pollutant-specific chapters. Most evidence linking the various human health effects to ambient levels of air pollution comes from the fields of clinical physiology, epidemiology and toxicology. A description is provided of the main features of these fields as they apply to assessing the effects of air pollution.

What is an adverse effect of air pollution?

WHO *(5)* and the American Thoracic Society (ATS) *(6)* have provided guidance on definitions of what constitutes an adverse effect of air pollution. ATS, for example, has identified a broad range of respiratory health effects associated with air pollution that should be considered "adverse". These range from death from respiratory diseases to reduced quality of life, and including some irreversible changes in physiological function *(6)*.

Since the publication of the second edition of *Air quality guidelines for Europe* in 2000 *(7)*, evidence on the effects of air pollution on health has evolved quite substantially. While most of the literature generated in this period focused on respiratory and cardiovascular events attributed to short- and long-term exposures, a new generation of studies suggests that the occurrence of effects is not specific to these outcomes *(8–21)* (see Table 1). Exposure to ambient air pollutants during pregnancy seems to be related to intrauterine growth restriction and preterm delivery *(22–26)*.

The frequency of occurrence of a health effect associated with exposure to air pollution is inversely related to its severity *(25)*. In the presence of exposure, the

Table 1. Health effects of air pollution

Effects attributed to short-term exposure
• Daily mortality
• Respiratory and cardiovascular hospital admissions
• Respiratory and cardiovascular emergency department visits
• Respiratory and cardiovascular primary care visits
• Use of respiratory and cardiovascular medications
• Days of restricted activity
• Work absenteeism
• School absenteeism
• Acute symptoms (wheezing, coughing, phlegm production, respiratory infections)
• Physiological changes (e.g. lung function)
Effects attributed to long-term exposure
• Mortality due to cardiovascular and respiratory disease
• Chronic respiratory disease incidence and prevalence (asthma, COPD, chronic pathological changes)
• Chronic changes in physiologic functions
• Lung cancer
• Chronic cardiovascular disease
• Intrauterine growth restriction (low birth weight at term, intrauterine growth retardation, small for gestational age)

Source: World Health Organization *(25)*.

proportion of the population affected by less severe outcomes is much larger than that affected by the more severe outcomes (Fig. 1). Subclinical or subtle effects, such as temporary deficits in lung function or pulmonary inflammation, may occur in most of those exposed while mortality may occur in a few. It is usually the more susceptible who suffer the more severe effects. Mortality is advanced by days, weeks or even longer periods in those already ill, and those with a pre-existing medical condition are more likely to be admitted to hospital or to visit an emergency department *(27–29)*.

The total impact of air pollution is then likely to exceed that contributed by the less frequent but more severe outcomes, and in some cases be dominated by the less severe but more frequent ones *(25)*. From a public health point of view, it is important to understand this relationship for several reasons. Assessment of premature mortality, which up to now has been the major driver of the policy processes, is but the tip of the iceberg, representing a small fraction of all effects associated with air pollution.

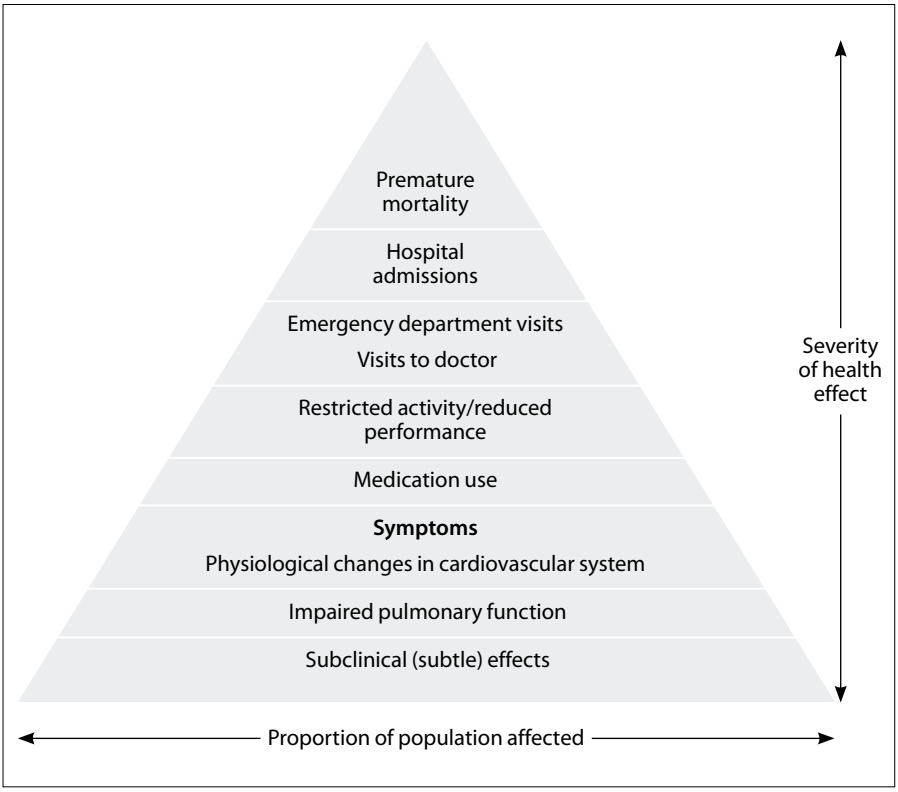
The attention paid to the more severe outcomes stems from their visibility and from the economic impact of outcomes such as mortality and hospital admissions. The first indications of adverse effects of air pollution on health actually arise from the marked increases in mortality following episodes of extreme air pollution *(1–3)*. While air pollution levels are currently quite low in comparison, mortality data are routinely reported in most populations in a fairly standardized way, thus facilitating their use in epidemiological studies and making mortality the most studied health effect. Furthermore, economic assessment of the health effects of air pollution often attributes the highest monetary value to mortality. Severe effects such as premature death, however, often occur in people already in poor health, and it can be assumed that they occur less frequently than less severe outcomes that affect a wider range of people. The frequency of the effects may be also determined by the proportion of people susceptible to certain pollutants (see Chapter 5).

Several studies have suggested that the exposure–response relationship between particulate pollution and mortality is essentially linear *(30–32)*. In a linear relationship, increasing exposures are associated with increases in the frequency of effects. An important implication of this apparent linear relationship would be the absence of a no-observable-effect level or limit value below which effects are not observed *(33)*. Thus, effects of pollutants occur even at very low levels, which may explain why a large proportion of the population is affected by air pollution. Besides the high frequency of less severe effects, such as demonstrated by changes in physiological parameters, it is important to consider that some of them may lead to chronic effects later in life *(34)*.

The exposure–response relationship has been explored in both Europe and the United States *(30–32)*. The shape of the exposure–response curve varies between locations. Sources of heterogeneity include different exposure profiles, climate

and individual population sensitivities to exposure *(31)*. In Europe, for instance, the exposure–response curves for ambient particles and total and cardiovascular mortality are steeper in southern European cities, while that for respiratory mortality is steeper in eastern European cities *(31)*. While there is a purpose in using several locations for the construction of exposure–response curves, current understanding of the reasons leading to heterogeneity may be insufficient to address subgroup differences.

Fig. 1. Pyramid of health effects associated with air pollution



Source: American Thoracic Society *(6)*.

In establishing threshold levels, it is important to consider that exploration of the shape of the exposure–response curve is based on data from short-term exposure studies. In these studies the exposure assignment is based on measures of daily average concentrations in the entire population of a given geographical area. Use of these broad measures of exposure as opposed to individual-level measures leads to misclassification of exposure for any given individual. Such misclassification would most likely cause an underestimation of the true effect *(25)*. In addition, the use of short-term studies ignores the impacts attributed to long-term exposures, which may be more representative of overall population

exposure than daily averages *(33)*. The exposure–response relationship has been investigated for other combinations of pollutants and health outcomes, though to a limited extent *(35,36)*.

The proportion of the population affected is determined by the prevalence of exposure. Air pollution is ubiquitous in urban areas, although levels of single pollutants may vary spatially within an area *(37)* and in many cities air pollution levels are still quite elevated. This is particularly the case in developing countries, where reported levels of air pollution exceed national and international standards *(38,39)*. The high population densities of urban areas lead to a large number of people being potentially exposed, and thus the number of individuals at risk of developing even subtle effects could be quite large.

The broad array of health effects associated with air pollution is partly explained by differential susceptibilities to pollutants, depending on both host and environmental factors *(40)*. Identifying the contribution of susceptibility to the occurrence of health effects from air pollution is key in determining who is most likely to develop adverse effects. Host factors include age, health status, diet and genetics. Environmental factors include exposure characteristics as well as the individual's housing and neighbourhood conditions.

Young children, for instance, are among the most susceptible to effects of air pollution *(40–42)*. Children have higher breathing rates than adults and therefore a higher intake of air pollutants per unit of body weight. They also spend more time outdoors than adults, thereby adding to their exposure potential *(42,43)*. The developing lung may have a limited metabolic capacity to address toxic insults. Since 80% of alveoli are formed postnatally, and changes in the lung continue throughout adolescence, exposure to air pollutants poses a serious risk to this population group *(43,44)*.

People with pre-existing cardiac or respiratory diseases are also more susceptible. Studies have shown that those with pre-existing disease are at higher risk of seeking medical attention or of using more medication to control their condition. For instance, increases in the use of asthma medication in children have been associated with ambient levels of air pollution *(14)*.

The pattern of exposure is influenced by many individual factors that are often interrelated. These include differences in time–activity patterns or habits, the micro-environmental concentrations of the area of residence, and housing characteristics *(40)*.

Another determinant of susceptibility seems to be socioeconomic status. There is a small but growing body of literature suggesting that economically disadvantaged population groups may experience a disproportionately higher health burden caused by air pollution *(45)*. An inadequate nutritional status, limited access to health care and higher exposures may be some reasons for the higher burden. Educational attainment, another indicator of socioeconomic status, has been reported to modify the effect of air pollution on respiratory and cardiovascular

mortality. Those with higher educational levels had the lowest mortality risks *(46,47)* (see Chapter 6).

Understanding of the biological mechanisms through which air pollution exerts its effects has evolved quite rapidly over the last decade, and several mechanisms are being proposed. Current evidence suggests that the effects of PM may be manifested through several, probably interrelated, pathways involving oxidative stress and inflammation. Oxidative stress has been hypothesized to be a common factor in a range of adverse effects of air pollution on the respiratory and cardiovascular systems *(48)*. Inhalation of PM can trigger inflammation in the smaller airways, leading to the exacerbation of asthma and chronic bronchitis, airway obstruction and decreased gas exchange *(49,50)*. PM can also interfere with the clearance and inactivation of bacteria in lung tissue, epithelial permeability and macrophage function, and may act as an immunosuppressor by undermining normal pulmonary antimicrobial defence mechanisms *(51,52)*.

The inflammatory response in the airways can also lead to effects on the cardiovascular system. The inflammation may induce transient hypercoagulability, progression of atherosclerosis and increased vulnerability to plaque rupture, especially in people with coronary atheroma *(53,54)*. More recently, the first evidence was presented that long-term exposure to air pollution may have a more proximate role in the atherogenesis process *(55)*.

Evidence is also accumulating in support of an effect of air pollution on cardiac autonomic control, leading to changes in heart rate variability and arrhythmia in susceptible individuals *(34,53,56–59)*.

The mechanisms of effect of other pollutants have not been as thoroughly studied but some gaseous pollutants, such as ozone and oxides of nitrogen, also share the property of being potent oxidants *(60)*. As for other health effects, such as adverse pregnancy outcomes, the biological mechanisms remain unclear. A more comprehensive analysis of the biological mechanisms through which PM, sulfur dioxide, nitrogen dioxide and ozone exert their health effects is available in Chapters 10–13.

Assessing the health effects of air pollution

Most evidence linking the various human health effects to ambient levels of air pollution comes from the fields of epidemiology and toxicology. This section consists of a description of the main features of these fields as it applies to the assessment of effects from air pollution.

Epidemiological studies

Studies of short-term exposure

The relationship between changes in air pollution levels over the short term and changes in various indicators of population health or health of individuals is studied in time series, panel and case-crossover studies.

Time series studies

Time series studies estimate the influence of temporal (usually daily) variations in air pollutant concentrations on mortality or morbidity, using statistical models linking the daily counts of health events in a geographically defined population with daily measures of air pollution and other time-dependent variables. It is by conducting studies using this type of design that most of the evidence of the role of air pollution in producing acute health effects has been generated. These include primarily studies of daily mortality, hospital admissions, and visits to emergency departments and primary care facilities *(9–11,16,61)*.

Increased access to health and air pollution data is one factor that has facilitated the implementation of time series methods in air pollution epidemiology. Mortality data are obtained from death registration agencies, while data on hospital admissions and visits to emergency departments and primary care facilities are usually obtained from computerized medical records. Access to air pollution data has been increased by the enhancement of air monitoring capacities in many urban areas of the world. This has made possible the assessment of effects of air pollution on relatively large populations, whose analysis would not be feasible if it required personal interviews to be conducted to obtain both health and exposure data. A large population size is necessary to ensure statistical power in situations where the magnitude of the individual effect is relatively small, as is observed when quantifying air pollution effects.

Another aspect determining the quantity and quality of time series studies is the substantial developments in statistical methods for time series analyses, particularly on the issue of controlling for potential temporal confounding by time-varying factors such as weather and seasonality. Inadequate controlling for these factors can lead to spurious associations, and this methodological drawback was the main argument used by those questioning its validity in the past *(62–64)*.

Flexible smoothing techniques such as the generalized additive models (GAM) *(65)*, which allow non-parametric smooth functions to control for the non-linear effects of season and temperature, have been introduced to provide a better fit to the data and thereby tighten confounding control *(66)*. This method first appeared in the air pollution literature around 1993 and has since become the standard approach in time series analyses *(67)*. Problems were identified in the application of GAM routines generated with a widely used statistical software product. This was responsible for an overestimation of the effects of air pollution on mortality in studies conducted with this software *(68)*. Problems in the generation of standard errors, leading to an incorrect estimation of confidence intervals, were also identified *(69)*. Both these problems generated a series of re-analyses of key studies, using alternative approaches, and have since been resolved *(11)*.

Methods have also been developed to obtain estimates resistant to short-term mortality displacement, reducing the possibility that the increased mortality

associated with higher pollution levels is restricted to very frail persons for whom death would be brought forward only a few days or weeks *(28,70)*.

Time series studies consider short-term exposures and, for this reason, are especially suited to examining the acute effects of air pollution. In fact, if there are short-term relationships (for example, air pollution has an effect on hospital admissions or mortality observed one or two days from the time of exposure) these can only be detected through daily analysis. In contrast, chronic effects of air pollution cannot be completely quantified with time series methods. Long-term exposure may increase individual frailty, but those who are frail might die at a time unrelated to an acute exposure and they are therefore not captured by a time series study.

One of the great advantages of the time series approach is that factors such as socioeconomic conditions, occupation or tobacco use cannot confound the relationship between air pollution and health effects, since these factors do not present daily variations. Moreover, the use of already collected health and exposure data reduces the costs associated with data collection, making this type of study less expensive to conduct than other epidemiological designs. Its lower costs make it easy to replicate in different locations.

Nevertheless, the use of data that have been generated for purposes other than research has some limitations. Issues with quality of health data include differences in diagnosis, recording and reporting, which introduce variability and may explain differences in individual risk estimates when comparing results from different studies *(39)*.

Pollutant concentrations used in studies usually come from established monitoring networks. Measurement methods, especially for ambient particles, differ among cities but specific practices are not always reported. This difference in methodology can influence the estimates obtained in time series studies *(71)*. In addition, the sources, levels and composition of the air pollution mix, as well as other individual exposure factors such as population mobility and daily activity patterns, may vary greatly from city to city and thus influence these estimates.

Overall, this design has advanced our understanding of the relationship between air pollution and health effects. It has allowed the exploration of effects associated with acute (and to some extent subacute) exposure durations in different population subgroups for different outcomes, facilitating the gathering of evidence and suggesting determinants of susceptibility. Finally, the consistent replication of results in many locations under different exposure conditions provides evidence in support of a causal relationship.

Panel studies

In such studies a group of individuals, ideally homogeneous, is followed up prospectively for a short period of time. Multiple measurements are obtained from each subject at different times and analysed using time series methods *(72)*.

This design has been employed to assess the association of short-term exposure to air pollutants with respiratory symptoms such as sore throat, common cold, cough, wheeze and shortness of breath, related medication use, and changes in pulmonary function *(73,74)*. The design allows the exploration of these outcomes on more susceptible individuals, such as those with underlying respiratory disease, children and the elderly.

Individuals are followed for a predetermined period, during which they record the daily occurrence of the outcome under investigation. One benefit of this design is the ability to obtain health- and exposure-related information from each individual, including a detailed health history, smoking history, socioeconomic status, and behavioural and time-activity patterns. Exposure information can also be obtained by means of personal monitoring, as the number of participants in panel studies is usually not large *(75)*.

Because exposure is common to all members of the panel, each individual serves as his or her own control, thereby eliminating the need for a control group. Only covariates that vary across time for a particular individual need to be controlled during the analysis *(74)*.

Meta-analysis

A meta-analysis consists of a statistical synthesis of data from a number of independent but comparable studies of a problem, leading to a quantitative summary of the pooled results *(76)*. Many efforts have been made to integrate the findings of time series studies, pooling results to identify overall trends in the influence of temporal variations in ambient particle concentrations on mortality or morbidity over a geographical area. Meta-analyses of panel studies have also been conducted *(73)*.

Some of these initiatives have been conducted through a multicentre approach, whereby protocols are developed to standardize all aspects of data collection and analysis. This approach ensures that data are highly comparable and that differences in results between individual centres are not explained by variability in study methods. In Europe, the APHEA-2 project used this methodology to estimate the influence of daily variations in various pollutants on mortality and morbidity for 29 cities whose data were later pooled *(77)*. A similar approach was undertaken in 90 American cities by the NMMAPS *(11)*.

Because time series studies have been conducted in many parts of the world, there is quite a large body of literature published by independent investigators. These results have also been pooled in order to identify overall trends. While the generation of quantitative summary estimates arising from these analyses did not benefit from a multicentre approach, steps were taken to make the results as comparable as possible. This was achieved by conducting a systematic critical appraisal of the studies, applying a predetermined set of criteria to ascertain study methods and data quality. WHO has formulated guidelines for the systematic

evaluation of epidemiological evidence *(78)*. Such quantitative summary estimates have been generated for Asia, Europe and Latin America *(38,39,73)*. Another such effort combined data from 109 studies conducted in different parts of the world *(79)*.

Quantitative summary estimates provide more robust information than data from individual studies, and therefore facilitate regional comparisons and the calculation of health impacts. One important problem in meta-analysis is the potential for publication bias, which refers to the tendency of editors (and authors) to publish articles containing positive findings rather than those that do not yield "significant" results *(76)*. Statistical techniques are available to assess this bias and should be used when conducting meta-analysis *(73,80)*.

Quantitative summary estimates are often used for estimating the costs and benefits of air pollution *(25)*. A limitation related to the usefulness of quantitative summary estimates for decision-making has to do with the heterogeneity of effect estimates from individual studies. Often in meta-analysis, effect estimates are pooled without consideration of the location of the individual studies. This may lead to the generation of quantitative summary estimates based on results that are not comparable. As observed with the development of exposure–response curves, more thought needs to go into how to address subgroup variations to enhance generalizability without losing power. Similarly, sources of heterogeneity include the air pollution mix, climate, and individual population sensitivities and demographics *(31,81)*.

Case-crossover analysis

The case-crossover study design was proposed by Maclure *(82)* to study the effects of momentary and intermittent exposures on the risk of developing an acute and rare health event supposed to occur soon after the exposure. Since this design focuses on individual deaths rather than death counts, it is possible to control for factors that may modify or influence the effects of air pollution on mortality at the individual level. Therefore, this approach has been applied in studies of the effects of air pollution on health as an alternative to time series analysis, since it may improve causal inferences about air pollution effects *(83)*.

The design can be seen as a variation on the case-control study, in which each individual bearing the event of interest (the case) acts as his or her own control. For each case, the distribution of exposures in the period just before the event is compared with the distribution of exposures estimated from some separate referent time period. Thus, by making within-subject comparisons, time-independent confounders are controlled by design.

When this design is applied to exposures that exhibit a time trend, however, there is great potential for confounding in the risk estimate owing to this trend in the exposure series *(84)*. Therefore, an important methodological feature of this strategy is adequate selection of control or referent periods. Several simulation

analyses have explored the potentials and problems of different strategies for sampling control periods *(85–87)* but, in general terms, they agree that they should be sampled bi-directionally, i.e. before and after the event.

Studies of long-term exposure

Cohort studies

This epidemiological design estimates chronic health effects associated with air pollution by examining risk of a health outcome (e.g. death) in relation to long-term average pollution exposure, usually by comparing people living in different geographical locations *(88)*.

Cohort studies usually provide larger estimates of pollution effects than time series studies, indicating that long-term exposures have a larger effect than short-term exposures *(88)*. This is because this design takes into consideration the full amount of time lost across all categories of cases attributable to air pollution (i.e. those whose underlying risk has been increased by long-term exposure and may or may not suffer the effect of an acute exposure, and those whose frailty is unrelated to chronic exposure to air pollution but whose death is triggered by an acute episode) *(89)*.

A key feature of this design is the availability of individual information on smoking status, occupation and other factors that can be potential confounding variables on a long-term assessment of the effects of air pollution on health. This allows one to obtain estimates adjusted for these potential individual confounders. They are also useful for assessing determinants of susceptibility.

The disadvantages of this type of study are the potential logistical difficulties and high cost of implementation, the follow-up of study populations over extended periods of time with great potential for losses, and the large numbers of subjects usually required to provide enough power. Moreover, as exposure is usually considered as a city-wide average, it is necessary to have several different locations to ensure adequate variability of exposure.

There are also difficulties related to the potential for uncontrolled confounding, which may limit the validity of the results of long-term cohort studies. If lifestyle characteristics, risk behaviour or environmental exposures other than air pollution are linked to city of residence of the study participants, and are also related to their risk of dying, then confounding would affect the results of these studies.

Most of the cohort studies in the air pollution literature have focused primarily on mortality and have provided the most complete estimates of the numbers of attributable deaths and the extent of the average reduction in life expectancy due to pollution exposure. They have therefore been considered most suitable for health impact assessment *(90)*.

Studies of effects of air pollution interventions

There have been some epidemiological studies that have attempted to evaluate the health effects of actions that have resulted in improved air quality. These include studies that examined the effects of interventions aimed at controlling and reducing levels of air pollution over urban areas *(91,92)* or studies of "natural experiments", i.e. interventions not designed for air pollution control but that have resulted in a reduction in pollution levels *(93–95)*. In general terms, these studies compare periods before and after the intervention and the impact of the observed reduction in pollution on the mortality and morbidity of the population.

These studies are important because information obtained from them provides strong support for a causal relationship between air pollution and health effects. Moreover, when evaluating interventions that produced sharp reductions in pollution levels over a relatively short period, the possibility of confounding by other risk factors is reduced. Nevertheless, only a few such studies have been conducted.

In Utah Valley, a reduction in air pollution levels caused by a year-long strike at a local steel mill was associated with reductions in total deaths and respiratory admissions *(93,94)*. During the Olympic Games held in Atlanta in 1996, city-wide changes in transportation patterns reduced vehicle exhaust and related air pollutants (such as ozone) by about 30%, the number of acute asthma attacks fell by 40%, and paediatric emergency admissions dropped by 19% *(95)*. Clancy et al. *(91)* examined the impact of a ban on coal sales in Dublin and found an 8% fall in mortality associated with a sustained reduction in average particulate air pollution. In Hong Kong, China, a restriction introduced over just one weekend, requiring that all power plants and road vehicles use fuel with a lower sulfur content, led to an immediate fall in ambient sulfur dioxide levels and a substantial reduction in seasonal deaths. The average annual trend in deaths from all causes declined by 2% and that in deaths from respiratory causes by 3.9% *(92)*.

Cohort studies with follow-up during periods of substantial change in air pollution can also provide an opportunity to assess the effect of recent vs past exposures. In an extended follow-up analysis of the Six Cities study, when there was an observed reduction in air pollution levels, Laden et al. *(17)* detected a reduction in overall mortality associated with decreased mean levels of $PM_{2.5}$.

The evidence provided by epidemiological studies designed to assess the health impact of substantial changes in air pollution levels is of considerable public health interest. To date, attempts to assess health impact have been based mostly on risk estimates obtained from other types of epidemiological study and applied in hypothetical air quality scenarios *(96)*. In most cases, however, these results have not been confirmed through comparison with studies of real interventions with clear reductions in air pollution.

The observed impact of the ban on using coal in Dublin was nearly twice as large as those predicted by models using estimates obtained from traditional

time series studies and applied to the observed scenario of air pollution reduction *(91)*. This again suggests that the time series approach does not capture the full range of effects attributed to air pollution exposure, which includes effects of short- and long-term exposures. Consequently, it will underestimate the benefits of outdoor air pollution control interventions.

Toxicological studies

By generating supporting evidence on the types of physiological effect exerted by air pollutants and the biological mechanisms underlying these effects, toxicological research has played an important role in advancing understanding of the associations between air pollution and mortality and morbidity reported in epidemiological studies *(97,98)*.

Much of the evidence contributed by the toxicological sciences on the effects of air pollution has been generated through inhalation studies, whereby human volunteers or animals are placed under controlled exposure conditions. When conducted in humans, such studies are also known as human clinical studies. It is through these studies that the assessment of subclinical respiratory and cardiovascular effects, such as changes in lung function, blood pressure and heart rate, has been possible *(97–100)*.

Controlled exposure conditions may lead to a more adequate assessment of biological mechanisms and dose–effect relationships than epidemiological studies. Under controlled conditions, the exposure is well-documented and standardized while study subjects are exposed to the same concentrations for similar periods. In addition, it is possible to assess effects from exposure to single pollutants or a mixture of pollutants. The assessment of single pollutants provides valuable information on individual mechanisms of action, while the study of mixtures is important because it may be a better approximation to "real" exposure conditions *(97,101)*.

Over the last decade, the development of technologies to concentrate particles derived from outdoor air has led to an improved understanding of effects of particles on health. The concentrator approach facilitates studies of exposure to fine (0.1–2.5 μm in diameter) and ultrafine (<0.1 μm) particles by collecting them from the environment without modifying their physical properties *(102)*. The advantage is that the particle composition to which subjects are exposed when using this technology better reflects the actual outdoor particle mix *(103)*. Because this type of technology is not as effective in concentrating gases, however, the study of integrated "real" exposure conditions is still incomplete *(99)*.

Epidemiological studies have shown that some population groups are more susceptible to the effects of air pollution. These include children, the elderly and those with pre-existing health conditions such as asthma, COPD and ischaemic heart disease *(99)*. Concern has been expressed that toxicological studies designed to assess effects of air pollution have been conducted on young, healthy

people who did not reflect the susceptible groups reported in the epidemiological studies. Recent studies have taken steps to address this limitation by recruiting volunteers with pre-existing conditions such as COPD or ischaemic heart disease, or patients with implanted cardioverter defibrillators *(104–107)*. Animals with experimental or genetically based cardiopulmonary disease, pulmonary hypertension, chronic bronchitis or asthma are also being used in toxicological studies *(103,108)*.

Data derived from human exposure studies allow researchers to avoid many of the uncertainties and problems arising from interspecies extrapolation. There are inherent anatomical and metabolic differences between animals and humans that must be considered when making inferences for humans from animal toxicological studies. These differences influence pollutant deposition patterns and fate in the respiratory tract and the concentration–response relationship, all of which are major determinants of effects and susceptibility *(109,110)*. Nevertheless, there are limits to the extent to which human volunteers can be exposed, since their participation in such studies should pose no threat to their health and life *(111)*. Similarly, some of the procedures for determining changes in health outcomes may be too invasive to be conducted in humans, and animal models may need to be used instead *(97,98,101)*.

Choice of study design

Although current evidence suggests that both long- and short-term exposures to air pollution are associated with health effects, the type of study design employed provides information on different aspects and this may have to be accounted for in analysing evidence and trying to establish causality. Long-term exposure exhibits larger effects with greater relative risks. Indeed, whereas most time series studies conducted to date have estimated relative risks of mortality of less than 1% per 10 $\mu g/m^3$ increase in air pollution levels over the previous days, cohort studies have revealed excess relative risk in the order of a 4–10% increase in mortality for the same change in air pollution on a long-term basis.

Time series and cohort studies are in fact measuring different aspects of the effect of air pollution on health. Using mortality as the end-point, time series studies capture only cases in which death has been triggered by a short-term exposure. This includes deaths among those whose frailty might or might not be related to long-term exposure. However, it does not take into account the death of those who became frail because of chronic exposure but whose time of death was not related to an acute episode. These are missed in a time series approach *(89)*. Consequently, this type of epidemiological design will underestimate the average reduction in life expectancy, an important measure of the public health impact of air pollution *(88)*.

On the other hand, cohort studies capture all categories of death related to air pollution, including individuals whose frailty was caused by chronic exposure.

Nevertheless, these studies cannot examine increased short-term risk of death among the frail population *(88,89,112)*.

For a proper assessment of the public health impact of air pollution, it is important to measure the extent to which shortening of the lifespan is attributable to short- and long-term exposure to pollution. Because cohort studies can estimate a change in age-specific mortality, they allow the ascertainment of life expectancy at a particular age *(112)*. For example, it has been estimated that the amount of shortening of life expectancy due to commonly observed levels of air pollution is around 1–2 years, which is substantial compared to the effect of other lifestyle or environmental risk factors related to mortality *(113)*. It is therefore recommended that public health estimates of the impact of air pollution on health be based on the results of cohort studies *(88,89)*.

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5. Determinants of susceptibility

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Summary

Individuals respond differently to exposure to air pollution, and features contributing to these variations have been accumulated under the concept of susceptibility. Increased susceptibility to air pollution has been linked to a large number of factors.

Higher death rates in response to exposure to air pollution are found in individuals already affected by chronic respiratory or cardiac diseases such as COPD, pneumonia and ischemic heart disease. Furthermore, type 2 diabetes substantially increases the risk. Augmented morbidity associated with exposure to PM has been observed in asthmatic people, including increases in symptoms, medication use and visits to hospital emergency departments.

Population groups with lower socioeconomic status have shown increased risk of mortality and morbidity following exposure. Higher susceptibility is also found in the least educated sections of the population and residents of deprived inner cities. In addition, people with lower socioeconomic status have more risk factors for the health effects of air pollution, for example airways diseases, active and passive smoking and type 2 diabetes.

Nutrition may also manipulate the health consequences of exposure. While overeating and obesity seem to increase the risk of diabetes, thereby enhancing the mortality risks of PM exposure, the strengthening of antioxidant defence systems, for example by dietary intake of antioxidants, may reduce the effects.

Epidemiological studies have generally not found gender differences in health effects of air pollution. Nevertheless, the possibility that gender has an influence on risk can currently not be excluded.

The biological mechanisms by which air pollutants exert their health effects include inflammatory and oxidative processes in the body. Gene polymorphisms, as found in inflammatory cytokines and antioxidant systems, influence responsiveness. Respiratory diseases caused primarily by genetic mutations, such as cystic fibrosis or alpha-1 antitrypsin deficiency, increase the risk of health effects from exposure to air pollutants. ▶

- The distribution of risk factors and modifiers, as well as diseases, age and other population characteristics and their change over time, affect the proportion of susceptible individuals in a society. Therefore, future considerations will have to account, for example, for the growth in the elderly population as well as for the global trend towards urbanization, with increasing numbers of people living in urban areas and the related increase in exposure to risk factors in the urban environment. The increased prevalence of diseases affecting immune susceptibility, including AIDS, will also result in larger proportions of the population having increased vulnerability to health effects from air pollution.

Introduction

There is considerable variability among individuals with regard to the health effects of air pollution. For example, short-term increases in ambient concentrations of PM_{10} result in increased mortality from both pulmonary and cardiovascular causes, but the majority of exposed individuals show no obvious effects. A clearer understanding of the individual characteristics that confer increased risk to the health effects of air pollution would (*a*) promote a reduction in risk for the most susceptible, either through avoidance of exposure or minimization of the risk factor(s) and (*b*) help in understanding the mechanisms involved.

The concept of susceptibility is highly relevant in assessing the health impacts of pollutant exposure *(1)* and this issue has been reviewed *(2,3)*. Our current understanding of individual susceptibility comes predominantly from four types of study: ecological, panel, animal exposure and human clinical studies.

Ecological studies often involve large populations, including individuals at the greatest risk. Sources of individual information in these studies may be death certificates or hospital discharge diagnoses, however, which provide limited individual information and are subject to misclassification of diagnosis or of cause of mortality or morbidity.

Panel studies assess acute health effects using a modified longitudinal design that combines cross-sectional and cohort study methods. The investigator conducts a series of cross-sectional studies of the same individuals or study sample. Small groups, or panels, of individuals are followed over short periods and health outcomes, exposure and potential confounders are ascertained for each subject on one or more occasions *(4,5)*. Panel studies provide the opportunity to better characterize the participants and to recruit subjects for the study of specific risk factors, such as underlying respiratory or cardiac disease, age or gender *(6)*. However, the sample size is limited by practicality, and those at the extremes of age or disease severity may be unable to participate.

Animal exposure studies permit careful control of experimental conditions and pollutant exposures, and allow longer-term exposures and dose–response characterization. An increasing array of animal models of human disease provides tools for investigating susceptibility. Studies on the health effects of air pollution have used animal models of asthma, COPD, advanced age, hypertension, cardiac disease and diabetes. Animal studies provide the ability to identify groups of genes regulating key responses *(7)* and to manipulate the function of specific candidate genes through transgenic technology. Animal studies are limited by difficulties in extrapolating animal diseases and responses to humans. Animal models often fail to reflect key characteristics of the human disease in question, and findings in animals may not always be relevant for humans.

Human clinical studies *(8)* involve the most relevant species. Exposure conditions and atmospheres can be carefully controlled, and subjects can be selected in order to study specific characteristics or risk factors. Nevertheless, the sample size is limited by practicality and it is often not possible to study safely those who are most susceptible. In addition, studies are limited to short-term, acute exposures and responses *(9)*.

We begin by discussing general susceptibility issues, and then explore the role of specific underlying diseases. The goal of this chapter is to provide a general overview of susceptibility, with a focus on recent evidence.

Who are most affected?

The likelihood of an adverse response to an inhaled pollutant depends on the degree of exposure to the pollutant and individual characteristics that determine the susceptibility of the exposed person. The relationship between exposure and response may take different forms, depending on the mechanism by which the pollutant causes disease. If some minimum degree of exposure is required to produce disease, then a threshold is present. For most inhaled pollutants, the evidence indicates increasing risk with increasing exposure.

Susceptibility refers to an altered degree of responsiveness, whether increased or decreased. In considering the combined effects of two factors, synergism is considered present if the combined effect exceeds that predicted by the sum or products of the risks produced by the two factors acting independently. For some risk factors and diseases, the synergism is multiplicative: the combined risk equals the product of the two independent risks. An example is the multiplicative effect of both smoking and asbestos exposure on the risk for lung cancer. Recently, diabetics have been found to be at greater risk of cardiovascular effects than non-diabetics following PM exposure. Analysis of data from Cook County, Illinois, for the years 1988–1994 revealed that the presence of diabetes doubled the particle-associated risk for hospital admission for heart disease *(10)*. A 10-$\mu g/m^3$ increase in PM_{10} was associated with a 2.01% increase in admissions for heart disease for diabetics, while non-diabetics had only a 0.94% increase in admissions.

Factors determining susceptibility may include inherent individual characteristics (e.g. sex, age, degree of airways responsiveness or presence of alpha-1 antitrypsin deficiency) and exposure to other agents that also have adverse effects on the same target organ (e.g. cigarette smoke or asbestos). Thus, many sections of the population have been considered at increased risk from air pollution. For example, during the dramatic London Fog of 1952, infants, the elderly and those with cardiac and respiratory diseases experienced a particularly high rate of mortality *(11)*. Laboratory exposure studies suggest that people with asthma or with coronary artery disease may experience adverse effects from exposure to sulfur dioxide *(12)* and carbon monoxide *(13)*, respectively, at lower concentrations than healthy persons.

Aspects of lifestyle may also increase the risk of an adverse effect from inhaled pollutants. Cigarette smoking impairs defence mechanisms and induces chronic inflammation and permanent structural damage in the lung. The combined effects of smoking and air pollutants may be additive or synergistic *(14)*. Exercise may increase the likelihood of an adverse effect by increasing the dose of pollutants delivered to target sites in the lung as ventilation increases to meet metabolic demands. Exercise increases the deposition fraction of ultrafine particles in the lung *(15)*, thereby further enhancing the increased dose of particles that occurs with the increased ventilation rates during exercise. People with obstructive lung diseases such as asthma or COPD often have greater deposition of fine particles in the lung than healthy people and the particles deposit more centrally in the airways, which means that some parts of the major airways may have much higher deposition of particles than others *(16,17)*. Mild asthmatics have a greater deposition of ultrafine particles than healthy people *(18)*. This may partially explain why individuals with underlying airways disease are more susceptible to the respiratory effects of air pollution.

Genetics

Gene polymorphisms influence responses to external agents *(7)*. The successful sequencing of both the human and mouse genomes, along with rapid technological advances in molecular biology, have made feasible a systematic search for the genetic bases of susceptibility to air pollution exposure. Furthermore, increased understanding of the mechanisms behind pollutant effects helps to inform the search for candidate genes. There is still much to be learnt about the nature of air pollution responses and their underlying mechanisms, and identifying genetic susceptibility factors provides mechanistic insight.

Extensive use has been made of the varying susceptibility of inbred mouse strains to lung injury and inflammatory responses to air pollutants, particularly ozone and PM *(7,19)*. The extensive homology between the mouse and human genomes means that the findings from these studies are likely to provide clues on potential susceptibility genes in humans. Candidate genes include tumour

necrosis factor-α (TNF-α), inflammatory cytokines, the toll-like receptors and antioxidant systems.

In humans, Bergamaschi et al. *(20)* observed that ozone-induced changes in pulmonary function and epithelial permeability were related to polymorphisms in genes for quinine metabolizing enzymes. These genes have similar linkages to those demonstrated in rodent models of exposure to ozone and PM *(7)*. Yang et al. *(21)* recently presented evidence that polymorphisms in the TNF-α gene influence lung function responses to ozone in humans.

One of the candidate genes most implicated in air pollution responses is glutathione S-transferase MU-1 (GSTM1). Glutathione S-transferase is an important enzyme in the glutathione pathway for protection against oxidant injury *(22)*. GSTM1 has a null allele with no protein expression, which confers reduction in antioxidant protection. This allele is present in 40% of the United States population. Children with the GSTM1 null allele have reduced lung function growth *(23)*. Children in Mexico City who carry the GSTM1 null allele appear to be more susceptible to the effects of ambient ozone exposure *(24)*. GSTM1 and GSTP1 polymorphisms may also play a role in enhancing the nasal IgE response to diesel exhaust particle exposure *(25)*.

There are genetic causes of respiratory disease that increase the risk of exposure to air pollution; two examples are cystic fibrosis and alpha-1 antitrypsin deficiency. Cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator protein. In a recent study *(26)*, a 10-μg/m^3 increase in $PM_{2.5}$ was associated with a 21% increase in the odds of having two or more exacerbations of acute respiratory symptoms. The ZZ and null phenotypes of the allele for alpha-1 antitrypsin confer a markedly increased risk for COPD, a disease that increases the risk of health effects from air pollution.

It is likely that the variability in extrapulmonary responses to PM exposure, particularly cardiovascular disease, is genetically influenced. Exposure to PM may alter blood concentrations of coagulation factors such as fibrinogen in some people, leading to small increases in the propensity for clot formation *(6,27,28)*. PM exposure increases clot formation in animal models of vascular injury *(29)*. Polymorphisms in the gene for Factor V are associated with an increased risk for myocardial infarction in young women *(30)* and enhance the risk associated with known risk factors such as smoking and diabetes. The common 4G/5G polymorphisms in the promoter region for plasminogen activator inhibitor-1 double the risk for myocardial infarction in diabetics. It seems likely that the presence of these polymorphisms would further increase the risk of myocardial infarction following exposure to PM.

Exposure to ambient PM has been associated with increased mortality from lung cancer *(31)*. The major risk factor for lung cancer is cigarette smoking, but genetic factors influence susceptibility *(32)*. Polymorphisms in drug metabolizing enzymes, especially the CYP enzymes, and mutations in the p53 tumour

suppressor genes have been the focus of interest. It is likely that genetic susceptibility also influences the risk of malignancy following PM exposure.

Socioeconomic status: population- and disease-based issues

The relationship between socioeconomic status and air pollution health effects was the subject of a workshop held in Boston, Massachusetts in 2002 *(33)*. A number of time series epidemiological studies have shown increased risk for mortality and morbidity in groups with lower socioeconomic status, and a large prospective cohort study has shown an increased risk of mortality from PM exposure among the least educated *(31)*. Some studies suggest that residents of economically deprived inner cities are at greater risk *(34)*.

There are two major explanations proposed for this increased risk: (*a*) lower socioeconomic status is associated with an increased level of exposure; and (*b*) people with lower socioeconomic status have more predisposing health conditions, types of behaviour or traits *(33)*. Both of these appear to be true, at least for some pollutants and health outcomes. People with lower socioeconomic status are more likely to live in polluted major cities and to live near roadways, industrial plants or other pollutant sources. Several studies have shown that exposure to combustion-related pollutants varies with indicators of socioeconomic status, including occupation, education, minority status and income *(33)*.

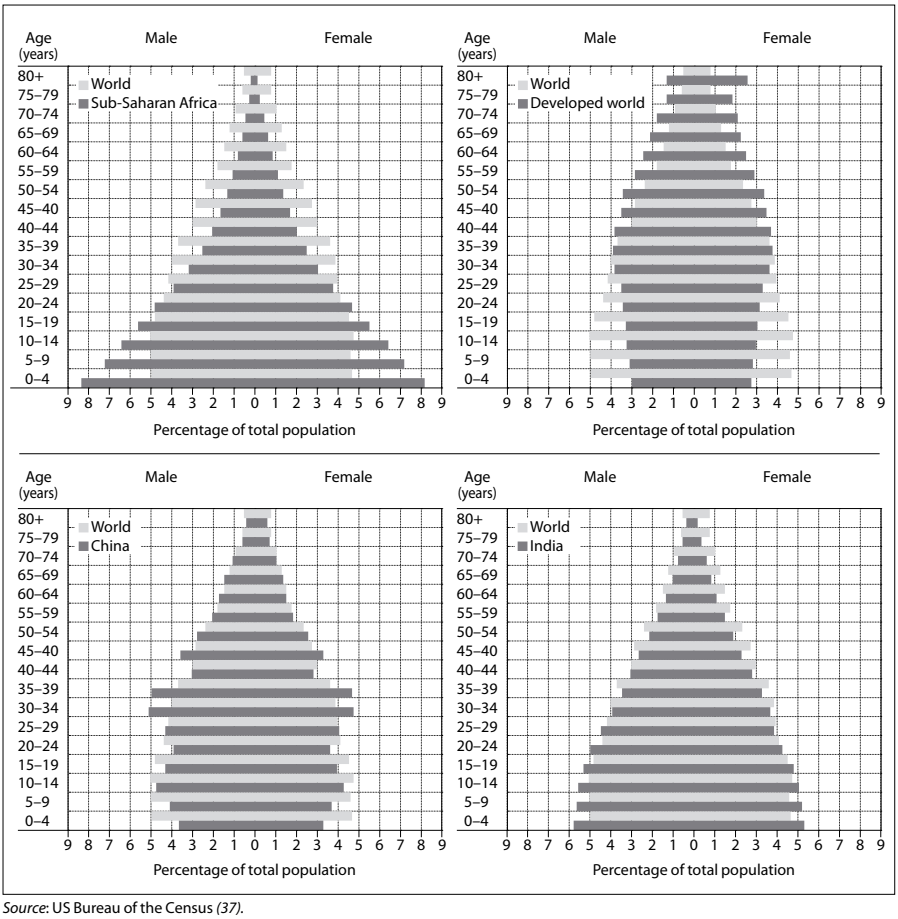
People with lower socioeconomic status have more risk factors for the health effects of air pollution. For example, the occurrence of airways diseases, smoking and exposure to environmental tobacco smoke is higher among central city residents in lower socioeconomic groups. Type 2 diabetes, recently recognized as a major risk modifier for PM health effects, is more common among the elderly, inner city residents, African Americans and Mexican Americans. Diabetes is more common in poorer countries *(35)*. Lower socioeconomic status is associated with reduced access to health care, nutrition and sanitation. There is often a complex interrelationship between these susceptibility characteristics and socioeconomic status, as described by O'Neill et al. *(33)*. Individuals may suffer major declines in socioeconomic status as a result of developing a chronic disease and becoming unable to work.

Underlying differences in age, disease and risk factor distributions may also affect susceptibility at the population level. Differences in population age structures alone will influence the proportion of susceptible individuals in a population. For example, developing countries typically have a much larger proportion of young children than more developed countries (Fig. 1). In addition, with the rapid growth in the number of elderly people in developing countries, particularly China and India, the age structure of the global population will change remarkably over the next half century. In China, people 65 years and older will outnumber those under 15 years of age by 2050 *(36)*, resulting in a corresponding increase in the burden of chronic diseases.

By 2030, the urban population in Asia will surpass the rural population *(38)*. This reflects a global trend in the increasing number of people living in urban areas and an increase in exposures to risk factors in the urban environment. Moreover, developing transportation, housing and other infrastructures for these new city dwellers is likely to result in additional sources of pollution *(39)*.

While a large portion of the burden of disease in developing countries is due to malnutrition, maternal conditions and communicable diseases, the incidence and prevalence of noncommunicable diseases continue to increase (Table 1). In addition to being related to the changing age structure of the population, this "double burden" is also due to the continued prevalence of "traditional" risk factors (such as indoor air pollution from solid fuel use and limited access to clean water and sanitation) along with the emerging prevalence of "modern" risk factors such as tobacco smoking *(40)*, sometimes referred to as the "risk overlap". An increased prevalence of diseases affecting immune susceptibility, including

Fig. 1. Selected population pyramids: regional versus world distributions



Source: US Bureau of the Census *(37)*.

Table 1. Top 10 disease categories in developing and developed countries, 2002

	Developing countries				Developed countries	
	High child, high or very high adult mortality		Low child, low adult mortality		Low child, low adult mortality	
	Disease or injury	DALYs (%)	Disease or injury	DALYs (%)	Disease or injury	DALYs (%)
1	HIV/AIDS	9	Unipolar depressive disorders	5.9	Ischaemic heart disease	9.4
2	Lower respiratory infections	8.2	Cerebrovascular disease	4.7	Unipolar depressive disorders	7.2
3	Diarrhoeal diseases	6.28	Lower respiratory infections	4.1	Cerebrovascular disease	6
4	Childhood cluster diseases	5.5	Road traffic injury	4.1	Alcohol use disorders	3.5
5	Low birth weight	5	Chronic obstructive pulmonary disease	3.8	Dementia and other central nervous system disorders	3
6	Malaria	4.9	Ischaemic heart disease	3.2	Deafness	2.8
7	Unipolar depressive disorders	3.1	Birth asphyxia/ trauma	2.6	Chronic obstructive pulmonary disease	2.6
8	Ischaemic heart disease	3	Tuberculosis	2.4	Road traffic injury	2.5
9	Tuberculosis	2.9	Alcohol use disorders	2.3	Osteoarthritis	2.5
10	Road traffic injury	2	Deafness	2.2	Trachea/bronchus/ lung cancers	2.4

Source: World Health Organization *(40)*.

AIDS, will also result in larger proportions of the population with increased susceptibility and vulnerability to the health effects of air pollution.

Health system performance can also affect population vulnerability, as access to timely and adequate treatment may influence the ability to minimize the impact of all illness, including illness related to air pollution *(41)*.

Age

The increases in mortality associated with particulate air pollution are greatest among the elderly. The prevalence of COPD and other chronic respiratory diseases increases with age. However, many physiological changes associated with aging may increase susceptibility to particle effects. Virtually all components of the respiratory system are affected by aging, including spirometry, diffusing capacity for oxygen, lung elastic recoil, chest wall compliance and inspiratory muscle strength. In addition, maximal oxygen uptake and maximal cardiac output decline with age. The elderly are more susceptible to respiratory infections, partly because of an age-related decline in specific immune responsiveness. The elderly may be more susceptible to particle exposure because of lifetime exposure to

environmental agents, including particulate air pollution, as well as previous respiratory infections. In one study, healthy nonsmoking volunteers 65–78 years of age had increased neutrophils, immunoglobulin content and interleukin-6 levels in bronchoalveolar lavage fluid compared to 20–36-year-olds *(42)*. Thus, even in the healthy elderly, years of exposure to external challenges may induce airway inflammation and thereby increase susceptibility to a subsequent challenge. Elderly individuals (60–80 years of age) without known coronary artery disease experienced significant reductions in heart rate variability (HRV) with exposure to concentrated ambient particles *(43)*.

Children and infants also appear to be at increased risk, in part because they exercise outdoors more than adults. Children are particularly susceptible to acute respiratory infections, which are the most common cause of death in developing countries. Evidence from a variety of studies suggests that exposure to air pollution increases the risk of acute respiratory illnesses in children, including pneumonia, and admission to hospital for respiratory illness *(44)*. Pollutants implicated include PM, sulfur dioxide, nitrogen dioxide and ozone. Proximity to traffic appears to be a risk factor for respiratory symptoms and asthma in young children *(45)*.

One study *(46)* took advantage of the Mount St Helens eruption and demonstrated that health effects are related to particle source. A total of 120 fourth- and fifth-grade students in Montana underwent spirometry before and after the Mount St Helens eruption in 1980. Peak levels of total suspended particles reached astronomical levels in the days after the eruption, with a peak 24-hour average of 11 054 $\mu g/m^3$. There were no effects on pulmonary function associated with these massive exposures to crustal-derived particles. However, when the children were again tested several months later, when air particles were primarily derived from urban pollution, a significant decline in the children's lung function was found in association with increased exposure to urban air particles.

More recent data have linked increased levels of air pollution with decreased lung growth in individuals aged 10–18 years *(47)*. High personal exposures to fine particles may even be associated with adverse effects on the developing fetus *(48)*.

Nutrition

Many disorders involving inflammation share a potentially common mechanism: tissue injury and activation from increases in reactive oxygen and nitrogen species. These issues have been reviewed *(49,50)*. Dietary intake of antioxidants has been proposed as a protection against a variety of illnesses, including the health effects of exposure to air pollution. Animal and human studies of ozone exposure support the concept that antioxidant molecules in the epithelial lining fluid of the lung react with inhaled ozone, serving as a protective barrier. For example, ascorbate in epithelial lining fluid is consumed by exposure to ozone and

nitrogen dioxide *(51)*. However, baseline concentrations of antioxidant vitamins in epithelial lining fluid do not predict responsiveness to ozone *(52)*.

In a randomized trial, Romieu et al. *(53)* provided antioxidant vitamin supplements or placebos to children with asthma in Mexico City, while monitoring their lung function and outdoor air pollution concentrations. In children in the placebo group with moderate or severe asthma, ozone exposure was associated with declines in the maximum mid-expiratory flow and peak expiratory flow. This was not seen in the supplemented group, suggesting protection by the antioxidants.

Romieu et al. *(54)* also studied the cardiac protective effects of dietary supplementation with omega-3 fatty acids. In 50 elderly nursing home residents, the relationship between indoor $PM_{2.5}$ levels and HRV was determined for 1 month. Subjects were then randomized to receive fish oil containing omega-3 fatty acids or soya oil as a control. Indoor $PM_{2.5}$ was associated with significant reductions in HRV and fish oil abolished the PM effect. The HRV effects of PM were also reduced by soya oil, but not significantly.

A clinical study *(55)* showed that, in young healthy adults on a diet deficient in vitamin C, antioxidant dietary supplementation reduced lung function decrements following ozone exposure but not the inflammatory response. This highlights the complexity of responses to pollutant exposure, and suggests that different effects may have different mechanisms.

Oxidants may also be involved in enhancing the allergic response. Whitekus et al. *(56)* showed that the thiol antioxidants N-acetylcysteine and bucillamine inhibited the diesel exhaust particle (DEP) induction of haeme oxygenase-1 in vitro. They went on to show that these antioxidants mitigated the adjuvant effects of DEP on allergen-induced IgE production in a mouse model.

Interestingly, dietary restriction in rats proved to be protective of the inflammatory effects of ozone exposure *(57)*. A 25% restriction in food intake reduced pulmonary injury from exposure to 2.0 ppm ozone for two hours. Levels of ascorbate and glutathione were increased in bronchoalveolar lavage fluid, and binding of ^{18}O-ozone was reduced. This suggests that dietary calorie restriction induced antioxidant production in the epithelial lining fluid, which consumed ozone more effectively. The effects of more severe or prolonged dietary restriction have not been studied. It is well established that significant protein and calorie malnutrition impairs the immune response and healing; the effects of malnutrition on susceptibility to pollutants is unknown.

Overeating and obesity may increase the consequences of air pollution exposure. Obesity increases the risk of diabetes; both are reaching epidemic proportions in some countries. Diabetes appears to enhance the mortality risks associated with PM exposure, as noted previously. In addition, obesity often leads to obstructive sleep apnoea, which can impair oxygenation and increase the risk of adverse cardiovascular events. The function of the vascular endothelium is key

to the development of atherosclerotic cardiovascular disease, and diet has major influences on endothelial function, both acutely and chronically *(58)*.

Gender

Air pollution exposure can adversely affect both males and females. Epidemiological studies have generally not found gender differences in effects, although few studies have been specifically designed to address this issue. Males and females have similar respiratory deposition of fine and ultrafine particles *(15,59)*, although fine particle deposition may be slightly greater in men when expressed per unit lung surface area *(59)*. Ozone-induced decrements in lung function are similar in men and women *(60)*.

A recent series of studies examined the respiratory and cardiovascular effects of exposure to carbon ultrafine particles in healthy and asthmatic men and women *(61)*. Although a few of the outcome measurements showed small gender differences, the overall results were not supportive of a conclusion that one sex was more susceptible than the other.

There are at present insufficient data to exclude the possibility that gender influences the risk for health effects from air pollution. There are obvious physiological differences between men and women. The incidence and prevalence of specific diseases differ, as do responses to some medications. There are measurable differences in specific aspects of the immune and inflammatory responses. For example, females have a higher $CD4^+$: $CD8^+$ blood lymphocyte ratio than males and their blood monocytes make more prostaglandin E_2 and less TNF-α when stimulated *(62,63)*. There are also differences in vascular endothelial function *(64)*.

Chronic diseases as determinants of susceptibility

Epidemiological studies suggest that the observed increases in mortality occur among individuals with underlying respiratory and cardiac disease, particularly COPD, pneumonia and ischemic heart disease. Recent studies also suggest that people with type 2 diabetes are at substantially increased risk *(65)*. Morbidity studies indicate that individuals with asthma are also adversely affected by exposure to particulate pollution, ambient particle concentrations being associated with increased symptoms, medication use and visits to hospital emergency departments. A number of studies indicate that individuals with the following diseases are put at risk by increased air pollution levels.

Chronic obstructive pulmonary disease

The term COPD encompasses various pathophysiological states associated with obstruction to air flow. The obstruction is relatively fixed, differentiating this condition from asthma, in which reversibility or variability in airflow obstruction is a cardinal feature. There are three main pathophysiological elements seen

in patients with COPD: chronic bronchitis, emphysema or acinar enlargement, and narrowing of small, distal airways *(66)*. The pathophysiology of these disease types may confer different susceptibilities to the effects of air pollutant exposure. However, the information available for analysis in epidemiological studies (generally death or a diagnosis on discharge) does not permit distinction between the types of disease.

Smoking is by far the most important etiological risk factor for COPD. Occupational exposures also contribute. Genetic deficiency of the α-1 protease inhibitor enzyme is another proven, but rare, cause. Other postulated risk factors include increased airways responsiveness to nonspecific stimuli, asthma, childhood respiratory infections and air pollution *(66)*.

The mechanisms by which particle exposure may cause adverse effects in patients with COPD have not been determined. However, insights may be gained by examining the factors that contribute to the frequent occurrence of exacerbations in COPD. One of the most important of these is infection. The airways of patients with chronic bronchitis are often colonized with microorganisms such as *Haemophilus influenzae* and *Moraxella catarrhalis*. These organisms rarely cause respiratory infections in healthy adults, but frequently participate in the worsening of COPD and chronic bronchitis, evidence that host defence mechanisms are impaired. Mucociliary clearance is slowed, leading to retention of secretions and bacteria. Exposure to particles and sulfur dioxide could increase susceptibility to infectious complications of COPD by further impairing mucociliary clearance, increasing adhesion of bacteria to epithelial cells, altering natural host resistance factors in epithelial cells or mucus as a consequence of epithelial injury, impairing the function of cells that fight infection in the lung, or impairing specific or nonspecific functions of the immune system. Exposure to ozone appears to alter particle distribution in the lung *(67)*, which may further increase the dose of particles to susceptible lung units. Such effects could also increase susceptibility to respiratory viral infections, important contributors to declining lung function and death in patients with COPD.

In a recent study in Los Angeles *(68),* 13 elderly patients with COPD and 6 healthy elderly people were exposed for two hours to 200 $\mu g/m^3$ concentrated ambient fine particles. Neither group showed effects on lung function. There were small reductions in arterial oxygenation, but no effects on heart arrhythmias or HRV. In this study, those with COPD did not appear to be more susceptible than the healthy subjects.

Asthma

In contrast to COPD, asthma is often a disease of the young; the incidence is highest in the first 10 years of life. It is a very common condition, affecting some 6–9% of the United States population. The hallmark features of asthma are reversible airway obstruction, hyperresponsiveness and inflammation. A

growing body of evidence implicates allergic sensitization in the etiology of asthma. Even in mild asthmatics, biopsies of the airways reveal evidence of inflammation *(69)*.

Asthma and COPD share several potential pathogenic mechanisms for particle effects, particularly epithelial injury, airway inflammation and bronchoconstriction. Viral infections often precipitate exacerbation of asthma, perhaps by interfering with the elaboration of bronchodilator substances by epithelial cells or by worsening the underlying airway inflammation. Viral respiratory infections such as influenza increase nonspecific airway responsiveness, which can persist for weeks. Airway responsiveness to nitrate particles has been shown to increase during influenza in otherwise healthy individuals *(70)*; impairment of antiviral host defence by particle exposure would therefore be expected to increase the frequency and severity of asthma exacerbation.

Considerable evidence suggests that particle pollution contributes to exacerbation of asthma. Atmospheric particles, including acid aerosols derived from sulfur dioxide emissions, have been linked with worsening of symptoms, reduction in lung function, increased hospital admissions for asthma and increased medication use *(71,72)*. In the early 1980s, Utell et al. *(73)* demonstrated that exposure to acid aerosols reduces pulmonary function in asthmatics, although the concentrations used were considerably higher than ambient. In a field study, Yu et al. *(74)* followed daily symptoms of wheeze and shortness of breath in 133 children with asthma; they observed an 18% increased risk of a symptom for each 10-$\mu g/m^3$ increase in $PM_{2.5}$. In a subsequent report from that study *(75)*, a 10-$\mu g/m^3$ increase in $PM_{2.5}$ lagged one day was associated with a 1.2-fold increased odds of having a more severe asthma attack and a 1.08-fold increase in the use of rescue medication.

Two studies found that exposure to acid aerosols, either followed by *(76)* or in combination with *(77)* ozone exposure, increased airway responsiveness to ozone in subjects with asthma, at concentrations of acid aerosol well below those known to cause changes in lung function or airway inflammation in the absence of ozone. Acid aerosols are formed in the atmosphere as a result of sulfur dioxide emissions, and thus these emissions may enhance the lung function effects of ozone exposure in people with asthma. There is suggestive evidence that certain kinds of PM exposure, such as diesel exhaust, may contribute to causing asthma in susceptible people. Nasal instillation of diesel exhaust plus allergen challenge enhanced local antigen-specific IgE production and isotype switching to IgE *(78)*.

Pneumonia

Atmospheric particle concentrations have been linked with hospital admissions for pneumonia among the elderly *(79)*. Pneumonia is a common complication of COPD, and is often the precipitating terminal event. All of the host defence

factors mentioned above for COPD could be important in particle effects on the risk of developing pneumonia: interference with host defence mechanisms would be expected to increase this common cause of respiratory morbidity and mortality. There is a lack of data that would allow assessment of particle effects on defence against specific pathogens important in humans, such as *Streptococcus pneumoniae*.

Cardiovascular disease

Exposure to fine PM in ambient air is associated with increased mortality and morbidity related to cardiovascular disease, an increase in PM_{10} concentration of 50 μg/m^3 being associated with a 3–8% increase in relative risk of death *(2,80)*. The strongest associations are seen for respiratory and cardiac deaths, particularly among the elderly. Because deaths from cardiovascular causes outnumber those from respiratory causes, most deaths attributable to air pollution are cardiac in etiology. The US Environmental Protection Agency has estimated that approximately 60 000 excess deaths occur annually as a result of particulate air pollution and the majority of these are from cardiovascular causes, including myocardial infarction, sudden death and congestive heart failure *(80)*. Determining the biological mechanisms involved has been identified as a high priority research need by the US Environmental Protection Agency and the US National Academy of Sciences *(81)*.

Evidence from recent epidemiological and clinical studies suggests that fine particle exposure has effects on cardiac function, and may trigger acute events. Panel studies of elderly residents have shown associations between ambient particle concentrations and reductions in HRV *(82–84)*. Reduction in HRV is considered a marker of a "sick" heart, and is associated with adverse outcomes in patients with cardiovascular disease, including heart rhythm disturbances and death.

A recent study raises the possibility of a relationship between ambient particle concentration and acute myocardial infarction. Exposure to $PM_{2.5}$ was found to be a significant triggering factor among 772 patients presenting with acute myocardial infarction in the Boston, Massachusetts area *(85)*. An increase of 20–25 μg/m^3 $PM_{2.5}$ was associated with increases in both acute (2-hour, odds ratio 1.48) and delayed (24-hour, odds ratio 1.69) risk for myocardial infarction. This finding could not be confirmed in subsequent studies *(86,87)*. Particle exposure was also associated with increased frequency of cardiac arrhythmias in patients with implantable defibrillators *(88)*. Clinical studies of subjects exposed to concentrated ambient particles have shown reductions in HRV and increases in blood fibrinogen *(89)*. These studies suggest that exposure to ambient fine particles influences autonomic regulation of the heart, and is associated with increased arrhythmias and myocardial infarction in susceptible patients with heart disease.

There is recent additional evidence, from both animal and human studies, indicating potential mechanisms by which PM may worsen cardiovascular

disease. Suwa et al. *(90)* utilized an animal model of atherosclerosis, the Watanabe hyperlipidaemic rabbit, to demonstrate that exposure to PM enhances the progression of atherosclerosis. Rabbits exposed to PM for four weeks showed evidence of systemic inflammation (bone marrow stimulation) and more rapid progression of atherosclerotic lesions in the aorta and coronary arteries compared with control animals. These experimental findings provide support for other observations linking exposure to ambient PM with systemic inflammation in humans *(91)* and development of atherosclerosis *(92)*. For example, PM air pollution has been associated with increases in blood c-reactive protein *(93)*, reductions in red blood cells *(94)* and increases in plasma viscosity *(95)*. All of these changes involve potential mechanisms for adverse cardiovascular effects of PM exposure.

Exposure to PM air pollution may also have acute effects on vascular function in humans. Investigators exposed subjects to concentrated ambient particles plus ozone, and demonstrated constriction of the brachial artery of the forearm immediately after pollutant exposure *(96)*. Inhalation of ultrafine carbon particles alters blood leukocyte expression of adhesion molecules and the lung diffusing capacity in humans *(97,98)*. These findings indicate that there are acute vascular effects of exposure to air pollution, providing a mechanistic link between PM exposure and cardiovascular effects in humans. When these studies are considered together with the numerous epidemiological studies linking PM with cardiovascular effects, both acute and chronic, there is now convincing and plausible evidence that PM exposure adversely affects cardiovascular health.

Particle exposure may also affect cardiovascular health indirectly *(2,99)*. For example, the obstructive sleep apnoea syndrome (a common condition with prevalence estimates ranging between 1% in Israeli industrial workers and 42% in an elderly nursing home population *(100)*) has well-known adverse cardiovascular effects. Relaxation of upper airway musculature during the rapid-eye-movement phase of sleep leads to upper airway obstruction, apnoea, decreases in blood oxygen and subsequent arousal. The low-oxygen episodes are often associated with changes in cardiac rate and rhythm, and increased risk of adverse cardiac events, development of pulmonary hypertension and cor pulmonale. Exposure to particulate air pollution could either worsen upper airway obstruction through nasal or pharyngeal irritation or enhance the severity of hypoxaemic episodes by increasing ventilation–perfusion mismatching. Many deaths from this disorder may be misclassified as cardiac deaths, and a small pollutant-related effect could potentially affect large numbers of susceptible individuals.

Lung cancer

Lung cancer accounts for some 1.2 million deaths each year worldwide, exceeding mortality from any other cancer in the developed countries *(40)*. In general, tobacco smoking has been linked with approximately 90% of lung cancers but

environmental factors, including outdoor air pollution and most notably diesel particulates, have also been a concern as these contain a variety of known human carcinogens. Indeed, urban outdoor air pollution has been estimated to contribute to 62 000 lung cancer deaths per year worldwide *(5)*. Furthermore, mounting evidence indicates that populations in less developed countries may have exposures to indoor and outdoor pollutants that exceed those in developed countries. Smith & Mehta *(101)* have estimated that an additional 16 000 deaths are attributable to indoor particulate pollution as a result of burning coal for heating and cooking.

In the largest study to date, the American Cancer Society included 10 749 lung cancer deaths during the period 1979–2000 *(31)*. A 10-μg/m^3 increase in $PM_{2.5}$ was associated with an 8–14% increase in the risk of lung cancer. The risk was higher in males than in females, higher in those with the least education, and surprisingly higher for nonsmokers than for smokers. The increased cancer risk remained significant after adjusting for all of these factors and for age, diet, body mass index, alcohol intake and occupation. In addition, more recent studies, taking into account smoking and other risk factors, have observed increases in lung cancer associated with ambient air pollution. Furthermore, the differences in exposure between two periods of analysis in the Harvard Six Cities Study demonstrated reductions in mortality from cardiovascular and respiratory causes but not from lung cancer, a disease with a longer latency period and less reversibility *(102)*. Despite the recent evidence indicating an impact of particulate pollution on lung cancer, especially in developing countries, important uncertainties remain as to confounding, errors in exposure estimates and the mechanism by which particles could either initiate or promote the development of tumours.

Future considerations

Areas of future research are likely to include pregnancy and pregnancy outcomes such as birth weight and prematurity; neurological diseases, given our increasing understanding of transport of particles to the brain; and perhaps systemic diseases such as lupus and rheumatoid arthritis that are characterized by alterations in immune function. The relationship between increased susceptibility, genes and environment will continue to be a highly productive area of investigation.

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6. Environmental equity

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Summary

Environmental equity refers to principles of social justice that promote the equitable distribution of the burdens and benefits of society. There is emerging evidence of inequities among the population in adverse health effects due to air pollution, as well as of links between the spatial distribution of pollution sources and the presence of certain population subgroups.

Respiratory and cardiovascular diseases are especially relevant to air pollution susceptibility throughout the world. People in countries and regions with a higher baseline prevalence of respiratory diseases may have a higher response to outdoor air pollution. In developing countries, the burden of acute respiratory illnesses and death among children under the age of five is likely to be greater for groups of lower socioeconomic position (SEP). Furthermore, most of the current burden of mortality due to heart disease and stroke is found in low- and middle-income countries. In addition to SEP, other modifiers of health effects have been described, such as age and educational attainment, but it is not yet clear whether these differences reflect differential vulnerability or disparity in exposure.

Spatial relationships between sources of air pollutants and the presence of certain population subgroups reveal environmental equity between and within countries and cities. Motor vehicle traffic is one important source of elevated local pollutant concentrations in urban areas throughout the world. Data are still limited, but some evidence suggests that people who live, attend school and/or work near local sources such as traffic may represent a substantial fraction of the urban population (10–40%, depending on the definition) and may tend to be of lower SEP than the general population. Greater relative impacts of air pollution on mortality risk associated with long-term exposure have been seen for persons of lower SEP, while evidence is mixed for such differences in acute effects on mortality and hospital admissions. However, when higher baseline rates of ill-health for low-SEP populations are taken into account, the absolute effects will be greater even when relative risks do not differ.

Moreover, hot spot areas and air pollution episodes in cities may add another disproportionate burden in certain localities already characterized ▶

- by higher pollution exposures and/or population subgroups of lower SEP.

Generally, the emerging data on environmental equity suggest that: (*a*) owing to the impact of local sources, urban subpopulations exist that have consistently higher exposure to ambient pollution than others; (*b*) areas of high exposure sometimes coincide with lower SEP; and (*c*) groups of lower SEP may be more responsive to air pollution and have lower baseline levels of health.

Introduction to concepts of environmental equity and justice

Air quality improvement requires decisions and approaches to be made that are responsive to the needs of each country and locality and that involve many sectors. This chapter provides context for national and local decision-makers wishing to address concerns about inequitable burdens and benefits related to distributions of air pollution concentrations, exposure levels and associated health outcomes. Land-use patterns and policies not specifically linked to environmental management are important determinants of air pollution levels and distributions. This is especially true in developing countries, where settlements occur in industrial zones and transport patterns and the siting of commercial centres may affect population health.

Environmental equity refers to principles of social justice that promote the equitable distribution of the burdens and benefits of society *(1)*, with specific emphasis on exposure to environmental toxicants and associated health impacts. These principles introduce an ethical component into air quality management, and are consistent with a recent EU sustainable development report that includes social equity and cohesion among its main objectives *(2)*.

We first clarify a few terms often used when discussing these ethical questions. *Equality* implies a focus on equal distribution of health (or exposure to air pollution), whereas *equity* is a normative term that explicitly addresses differences between social groups in terms of health, access to health-promoting services and goods *(3)*. The term *environmental justice* encompasses questions of both the distribution of environmental exposures and procedural justice *(4)* and recent policies and regulatory actions have been inspired by environmental justice principles. The state of California *(5)* has called for "the fair treatment of people of all races, cultures, and incomes with respect to the development, adoption, implementation, and enforcement of environmental laws, regulations, and policies" and New York State now incorporates environmental justice concerns into the state environmental permit review process *(6)*. The US Environmental Protection Agency has provided guidance for the National Environmental Policy Act, which covers distributional and procedural justice *(7)*. In South Africa, the 1996 Constitution describes everyone's right "to an environment that is not harmful to

… health or well-being" *(8)*. Intranational, international and intergenerational justice are also important concepts in this field.

The historical context of the environmental justice movement, and research and action approaches inspired by it, are relevant for air quality management that addresses equity concerns. The environmental justice movement began in the 1970s in response to documented inequities in pollution exposure and consequent health effects *(9)*. This movement led to a new emphasis on community-based participatory research *(10,11)*, which brings researchers and affected communities together to design and conduct analyses that can then inform local decisions and policies. Participatory research traditions arose in Latin America, Asia and Africa and are strongly linked with the idea that knowledge be translated into action and social change *(12)*.

Environmental exposures are just one of the determinants of health that may contribute to socioeconomic gradients in health patterns *(13,14)*. These gradients have been observed in many countries using many different indicators of SEP. SEP is conceptualized and evaluated at both the individual level (e.g. educational attainment) and area level (e.g. neighbourhood of residence), both of which can independently influence health. Both material deprivation and psychosocial stressors may contribute to observed gradients by these indicators. Different SEP indicators (education, income, average educational attainment in a given area) might mean different things, depending on cultural context, gender and other social factors. Several research challenges addressing the effects of neighbourhoods on health have been recently identified, and are relevant to studying the interaction of air pollution exposure, socioeconomic context and health *(15–18)*.

This chapter uses the term environmental equity with the intention of focusing on evidence about the distribution of air pollution exposures and associated health effects and the relevance of these distributions to air quality guidelines. Research on environmental equity is concerned with identifying and reducing environmental exposure burdens that are often borne disproportionately by certain neighbourhoods, communities, countries and demographic groups (as defined by age, race, ethnicity and gender) owing to economic and other forces *(19)*. Disproportionate risks to health from air pollution may occur in low-SEP populations, either through higher exposure or through greater susceptibility. Evidence is mounting that both factors play a role. To ensure that research on SEP-patterned air pollution exposure and health differences is relevant to policy, the conceptualization and interpretation of individual- vs area-level SEP variables needs to be carefully considered, along with limitations in causal inference such as the potential for cross-level confounding *(20)*.

Policy contexts relevant to environmental equity

This chapter describes how concerns about environmental equity relate to air pollution risk assessment and policy development in both the developed and

developing worlds. Considerations of environmental equity may arise in several different air pollution policy contexts, including the permitting of new pollution sources, the development and enforcement of air quality management plans and land-use regulations, the assessment of health impacts, and the setting of air quality guidelines. While the present publication is concerned primarily with air quality guidelines, which provide concentration levels and/or risk assessment methodologies for determining safe levels of air quality for population health, environmental equity concepts are relevant to other air pollution policy questions. These include differences across population subgroups with respect to distributions of emissions, concentrations, exposure levels and associated health outcomes.

Air pollution risk assessment has played an important role in national and international assessments of the burden of disease related to air pollution *(21–23)* and in policy analyses of air regulations *(24)*. To date, environmental equity has not typically been taken explicitly into account in these analyses. This is due in part to the coarse spatial scales at which current air quality models typically operate for countrywide analyses. But it also reflects the common assumption that a single concentration–response (C–R) function can be used to link air pollution with adverse health outcomes regardless of population SEP or demographics. Levy et al. *(25)* demonstrated that the health benefits of controlling air pollution emissions can in fact be greater for low-SEP population subgroups when differential susceptibility and baseline health status are explicitly taken into account in risk assessment. These findings are also relevant to site-specific evaluations of the effects of air pollution sources (such as debates over the siting of incinerators) where considerations of environmental equity are increasingly relevant.

To illustrate the role that assumptions of environmental equity can play in health impact assessment, consider an analysis that compares potential health impacts of alternative policies for $PM_{2.5}$ reduction. One policy might reduce emissions from power plants and result in a reduction in $PM_{2.5}$ concentrations of 1 ug/m^3 across an urban area with a population of 1 million. Assuming a constant baseline mortality rate and a constant C–R function for the entire area, the total reduction in mortality risk (i.e. reduced numbers of expected deaths) is constant across the area. However, if differences in baseline mortality rates and C–R functions, associated with differing SEP, are taken into account, the estimated risk reduction is greater in locations with lower SEP *(25)*. Now consider an alternative policy that would reduce emissions of diesel exhaust particles, resulting in a 10-ug/m^3 reduction in $PM_{2.5}$ for the subgroup of 100 000 persons living along roads in the same urban area. If considerations of environmental equity are not taken into account, the overall risk reduction from this policy would be roughly the same as before, since the exposure reduction was 10-fold greater but the population was 10-fold smaller. Based on this analysis, policy-makers may view the two alternative policies as equivalent. However, if those who live near roads have

a lower SEP (and as a result have higher baseline mortality rates and steeper C–R functions) the potential benefits of the diesel policy vis-à-vis mortality would be substantially larger.

One goal of this chapter is to review findings from the air pollution and health literature to identify the strength of current evidence for differential exposures and health effects for people of different SEP. Several other important issues in health impact assessment for PM that may have implications for environmental equity are not directly dealt with. One is whether the C–R function differs for different PM components and/or sources. Another is the possibility that the PM C–R function has a different slope at concentrations well above those observed in the current epidemiological literature, most of which has been based on data from cities in the developed world.

Evidence of inequities in health effects of air pollution

It has been widely noted that persons of lower SEP have generally poorer health status than more advantaged persons *(26–28)*. Explanations for these differentials have usually focused on factors such as limited access to high-quality health care, inadequate nutrition, psychosocial stress, poor-quality drinking-water, alcohol misuse, exposure to indoor pollution, smoking and exposure to factors at the workplace *(29–31)*. Link & Phelan *(26)* draw attention to a broader set of contextual factors, including limited knowledge, money, power, prestige and beneficial social connections, which together serve to reduce the poor people's ability to manage their own health risks *(26)*. The relationship between low SEP and ill-health is relevant to the issue of environmental equity, because susceptibility to the health effects of air pollution may be greater among those with an already compromised health status. Indeed, there is substantial epidemiological support for this notion, going back to the distribution of health responses during the London Fog of 1952 *(32)*. If sick people are more responsive to air pollution (i.e. higher relative risk per unit increase in exposure) and poor people are more likely to be sick, then it would follow that poor people are on average more responsive to a given concentration of air pollution than more economically advantaged persons. It should be noted that, even if relative risks are constant, absolute impacts of air pollution will be elevated in populations with a higher baseline prevalence of mortality or morbidity.

Respiratory and cardiovascular diseases are especially relevant to air pollution susceptibility. In developing countries, acute respiratory illnesses (ARI) are the major cause of illness and death among children under five years of age *(33)* and the burden is likely to be greater for groups with lower SEP within those countries *(34)*. Romieu and colleagues *(33)* note that "ARI is the most common cause of illness and death in children in the developing world" and is responsible for 3–5 million deaths annually among children under five years of age. Indoor air pollution from biomass combustion is thought to contribute to this burden of

disease *(35,36)*, as described in Chapter 9. COPD among adults is also associated with indoor biomass combustion *(36)*. Exposures follow SEP gradients *(37)*. Countries or regions with a higher baseline prevalence of respiratory diseases may have higher responses to outdoor air pollution. Within urban areas in the United States, asthma morbidity and mortality rates are higher in less advantaged minority neighbourhoods than in more advantaged neighbourhoods *(38)*.

Cardiovascular disease is a leading cause of death and disability throughout the world *(22,39)*. Heart disease and stroke are currently responsible for some 17 million deaths a year, and this number is expected to rise to 24 million by 2030. Together with COPD, these diseases are responsible for 14.9% and 13.2% of disability-adjusted life years (DALYs) throughout the world *(22)*. Most of the current burden of mortality due to heart disease and stroke is in low- and middle-income countries. Whereas cardiovascular death rates have been falling in the developed world, the opposite is true in the developing world. Because pre-existing cardiopulmonary disease has been established as a susceptibility factor for air-pollution-related premature mortality, these trends may translate into differential air pollution risks.

A small but growing body of literature reports direct investigations of whether SEP or demographic factors modify the health impacts of air pollution. Age has been shown to modify the effect of air pollution on acute mortality, with larger relative (and absolute) impacts among the elderly *(40,41)*. Several acute effects studies suggest that populations with lower SEP exhibit enhanced responses to air pollution *(42–44)*. For example, day-to-day associations between death counts and air pollution were reported to be more pronounced in low-SEP communities in Canada *(42)*. In the city of São Paulo, Brazil, relative risks of PM_{10} on respiratory mortality in the elderly were higher in regions with lower socioeconomic conditions *(43)*. However, other studies examining the influence of socioeconomic conditions on relative risks for acute effects have not observed significant differences *(41,45–47)*. The association between long-term exposure to PM and increased mortality risk reported in cohort studies has been shown to be modified by indicators of SEP *(48–50)*. In the American Cancer Society cohort study *(48)*, the effects of $PM_{2.5}$ on mortality were greatest for those who lacked a high school education. There was essentially no evidence for associations between $PM_{2.5}$ and cardiopulmonary or lung cancer mortality for persons with education beyond high school. However, it is not yet clear whether these differences reflect differential vulnerability or differences in exposure. Individuals with less education may be exposed to higher PM levels than measured at the central site monitors, or the nature and mixture of pollutants may be different. As a whole, the evidence on differential responses to air pollution as a function of SEP remains inconclusive. More studies specifically designed to test this hypothesis are needed.

Considerations of environmental equity may emphasize the benefits of expressing health effects in terms of attributable cases rather than relative risks

(45). Most epidemiological studies of air pollution, and the policy summaries that derive from them, typically focus on relative risk, i.e. the percentage change in health outcome per unit change in air pollution concentration. This expression of health impact is conveniently obtained from the statistical models used in epidemiological studies. In comparing effects in different populations, however, policy-makers may find that health impacts expressed as attributable cases (i.e. number of cases of death or disease that are due to air pollution) are often more meaningful than the relative risks commonly reported. Attributable cases can be computed by multiplying the relative risk by the baseline rate of the health outcome in the affected population. If baseline mortality or morbidity rates are higher in one population than another, the number of cases attributable to air pollution will be correspondingly elevated, even if the relative risk is the same in the two populations. It is important for policy-makers to be aware of the distinction between the relative and absolute effects of air pollution on population health, and to consider which formulation is more appropriate in a particular policy context.

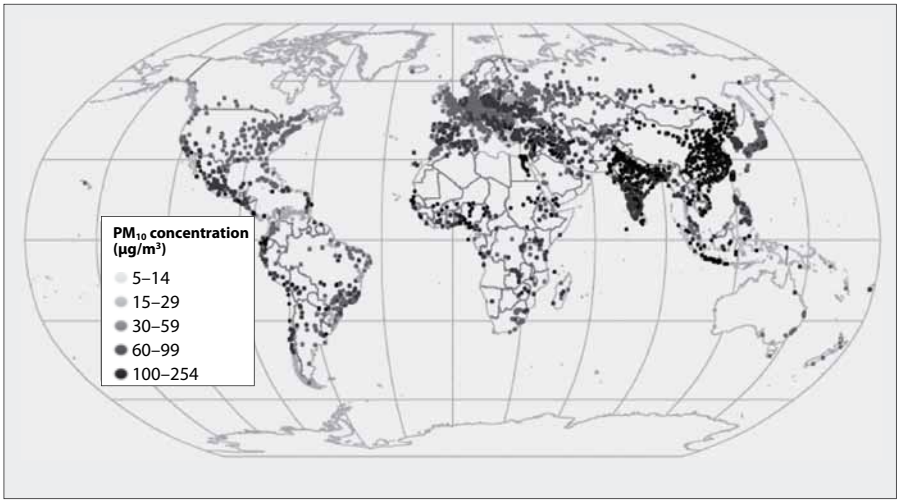
Evidence on the links between pollution sources and inequity

The spatial relationships between noxious sources and population subgroups as a function of SEP, and the enhanced exposure burdens that result, are complex but important environmental equity issues *(19)*. The underlying social, political and economic causes of disparate exposure burdens, and the possibility of compensating benefits, are beyond the scope of this chapter. Rather, we will review evidence from studies that examine spatial relationships between sources, concentrations and population groups. Personal exposures depend partly on ambient concentrations but also on indoor air pollution sources, housing characteristics and time–activity patterns. Although considerations of environmental equity are likely to apply to these exposure modifiers, for the sake of brevity this chapter focuses mainly on patterns of ambient concentrations rather than on personal exposures.

Environmental equity can span differences between countries, between cities and within cities. International differences are illustrated in Fig. 1, which shows the distribution of estimated annual average PM_{10} concentrations for cities with populations of more than 100 000 and for national capital cities. This figure makes clear that the less developed countries generally have higher particle levels than highly developed countries, implying strong intercountry environmental equity effects.

Within-country concentration gradients also appear to be pronounced, and reflect gradients of urbanization. Spatial gradients in air pollution within urban areas, especially those related to motor vehicle exhaust, have been highlighted by much recent research *(51–56)*, which has shown elevated concentrations of primary pollutants such as carbon monoxide, black carbon, nitrogen oxides and

Fig. 1. Estimated annual average concentrations of PM_{10} in cities with populations over 100 000 and in national capital cities



Source: Cohen et al. *(22)*.

ultrafine PM near roads with heavy traffic. Motor vehicle traffic is one important source of elevated local air pollution concentrations between and within urban areas throughout the world. Because intra-urban exposure gradients due to motor vehicle traffic are important for health, characterizing the magnitude of those gradients (i.e. quantifying the average incremental exposure burden imposed by living near traffic) is a key research need. This information is relevant to environmental equity to the extent that persons living, working or attending school near roads differ from others in terms of SEP, race or other factors.

Most available data on air pollution gradients near roadways derive from studies in developed countries. Fischer et al. studied concentration patterns for traffic-related pollutants in the city of Amsterdam *(52)*. Ambient air monitoring was carried out at ground level next to 36 homes, half along streets with high traffic flows and half along streets with low flows. They reported twofold differences in the concentrations of several traffic-related primary pollutants (black carbon, benzo(*a*)pyrene and benzene) between the locations with high and low traffic flows. The differences were less pronounced, in the 15–20% range, for PM_{10} and $PM_{2.5}$. The spatial patterns in concentrations for the traffic-related pollutants were highly correlated with one another (0.80–0.90), confirming their common source.

Routinely collected air monitoring data from Amsterdam were stratified into traffic-oriented vs background sites by Roemer & van Wijnen *(57)*. Average concentrations over a two-year period for black smoke, carbon monoxide, nitric oxide, nitrogen dioxide and ozone are shown in Table 1. Traffic-oriented sites had average concentrations for the primary pollutants (black smoke, carbon

monoxide and nitric oxide) that were two or more times larger than those measured at background sites. Secondary pollutants (nitrogen dioxide and ozone) showed smaller or inverse patterns of differences.

Table 1. Concentrations of air pollutants in Amsterdam, averaged over two years

Pollutant	Mean for traffic sites ($\mu g/m^3$)	Mean for background sites ($\mu g/m^3$)
Black smoke	21	10
Carbon monoxide	1805	836
Nitric oxide	130	28
Nitrogen dioxide	65	46
Ozone	36	43

Source: Roemer & van Wijnen *(57)*.

Kinney et al. *(51)* and Lena et al. *(53)* reported 2- to 4-fold contrasts in street-side black carbon concentrations across a range of traffic densities in New York City, but much smaller contrasts for $PM_{2.5}$. Measurements were carried out on pavements adjacent to streets, thus reflecting greater effects than would have been experienced in nearby buildings. Janssen et al. *(54)* stratified schools in relation to traffic measurements. They observed a 4- to 5-fold range in traffic volumes and a 2.5-fold range in black smoke concentrations; the range was smaller for $PM_{2.5}$. Previous work in the SAVIAH study for nitrogen dioxide showed contrasts in the 20% range with stable spatial variance that appeared to relate strongly to road traffic in Amsterdam, Huddersfield (United Kingdom), Poznan (Poland) and Prague *(58)*. The smaller gradients observed for nitrogen dioxide may be due in part to the locations sampled but may also reflect the secondary nature of nitrogen dioxide, which is formed downwind of the primary emissions of nitric oxide from motor vehicles. Together, these studies suggest that intra-urban traffic variations may lead to contrasts in air concentrations of about 2-fold for local traffic-generated primary pollutants such as black carbon, carbon monoxide, nitric oxide and benzene, and closer to 20% for pollutants that have a secondary and/or regional character, such as nitrogen dioxide and the sulfate and nitrate components of fine particles. These results suggest that considerations of environmental equity related to disproportionate exposures are more related to primary than to secondary pollutants. The significance for health of road emissions has been highlighted by several recent studies, suggesting that the mix of particles and co-pollutants emitted by motor vehicles may be especially potent *(49,54,57,59–61)*.

Intra-urban spatial gradients in pollution are likely to be even more pronounced in cities in the developing world than in those in the developed world studied to date, owing to higher emission rates from motor vehicles, industrial facilities and other localized pollution sources. Unplanned urban slum

communities often arise in or near areas designated for industrial use. These exposure burdens may be enhanced by the indoor use of biomass cooking fuels *(62)*. Few data exist to document exposures in cities in developing countries; research is urgently needed to document patterns and scales of intra-urban gradients in air pollution and to examine relationships between exposures and SEP in such cities.

The evidence pointing to localized effects of motor vehicles and other local pollution sources on air quality implies that subgroups of people in urban areas, by virtue of the location of their place of residence, school and/or workplace, receive higher average exposures than do others. One might argue that this unequal exposure burden is of policy concern regardless of whether it can be shown that the people with higher exposures differ from others in terms of SEP, race or other characteristics. If, on the other hand, SEP characteristics do coincide with source proximity, the moral case for reducing the environmental burden on groups that experience several types of disadvantage would be even stronger. The proportion of the population affected by local air pollution sources is likely to vary substantially between countries and between regions within countries, owing to different patterns of urban development, land use and transportation.

One approach to quantifying the population disproportionately exposed to air pollution from local sources might involve counting those living within a specific distance of major roads, industrial facilities and other sources in various cities throughout the world. Nerrière and colleagues *(63)* carried out an analysis of this type for four French cities: Grenoble, Rouen, Paris and Strasbourg. The proportion of city residents over the age of 30 who lived within approximately 100 metres either side of a road carrying more than 10 000 vehicles per day ranged from 40% to 61%, whereas the proportion near industrial facilities ranged from 3% to 18%. Nicolai et al. *(60)* used the ISAAC survey of 4777 Munich children aged 5–7 and 9–11 years, along with traffic counts, to calculate that about 16% of children lived within 50 metres of a road carrying heavy traffic (definition not given). Roemer & van Wijnen *(57)* stated that approximately 10% of Amsterdam residents lived along busy roads, i.e. those with more than 10 000 vehicles per day. In Nottingham, England, Venn et al. *(61)* assessed the proximity of homes to main roads for 6147 primary school children (4–11 years) from a case–control study and for 3709 secondary school children (11–16 years) from a random cross-sectional survey. Some 25% and 23% of the homes, respectively, were within 150 metres of a "main road" (volume not specified) and 3.5% and 3.4%, respectively, were within 30 metres. While not addressing the demographic characteristics of the affected populations, these studies suggest that substantial proportions of urban residents live in close proximity to roads with high volumes of traffic. However, because of differences in the definitions used, it is not yet possible to draw any firm quantitative conclusions. Standardized definitions of road volumes should be used in future studies.

While data are limited, racial and socioeconomic characteristics have been shown to differ in relation to source proximity. Green and colleagues *(64)* enumerated all state schools in California that were within 150 metres of a road with heavy traffic (at least 50 000 vehicles per day) and examined the racial and socioeconomic characteristics of students attending the schools. A total of 78% of students at the schools near heavy traffic were non-white, compared to 60% for schools near very light traffic. Similar differences were seen for indicators of socioeconomic disadvantage. Finkelstein and colleagues *(50)* reported higher levels of TSP and sulfur dioxide in areas with lower socioeconomic conditions in Hamilton, Ontario, presumably due at least in part to motor vehicle emissions. Affluent neighbourhoods may also be heavily affected by local sources such as roads.

Hot spots, episodes and cumulative impacts

An urban hot spot is an area within a city where long-term average concentrations of one or more air pollutants are consistently high compared with other areas of the same city, thus imposing a potential excess health risk burden. The hot spot is an especially relevant concept for environmental equity; it implies disproportionate burdens in certain locations, and the places where people live and work are often affected by socioeconomic forces. The significance for health of hot spots may be enhanced where one or more sources contribute a variety of pollutants to the mix of exposures. Cumulative effects of several pollutants often are not addressed by regulatory approaches that emphasize the control of individual pollutants. To the extent that multiple pollutants are at concentrations close to their guideline levels, the significance for health will be enhanced. Pollutant indices that take into account concentrations of multiple pollutants are one approach to addressing this gap.

The hot spot issue is related to, but distinct from, that of the pollution episode. Whereas a hot spot is characterized by spatially localized elevations in concentrations that are relatively stable over time, an episode is characterized by temporally localized elevations in concentrations that are relatively stable over space. Episodes most often occur as a result of unusual meteorological conditions that limit the dispersion of locally generated pollution emissions, but an episode will be exacerbated when there are also unusually large releases of pollution from one or more nearby sources. Cumulative effects of multiple sources are of special concern, and may be especially significant for residents and workers closest to the sources.

Regional air pollution episodes may lead to enhanced concentrations at hot spots. Day-to-day variations in air pollution concentrations experienced in urban areas are usually driven by regional-scale weather phenomena, which alter the degree of dispersion of the locally generated pollution and/or the degree of delivery of pollution generated at a distance. When stagnant weather conditions occur (i.e. low wind speed and low mixing height), proportional increases in

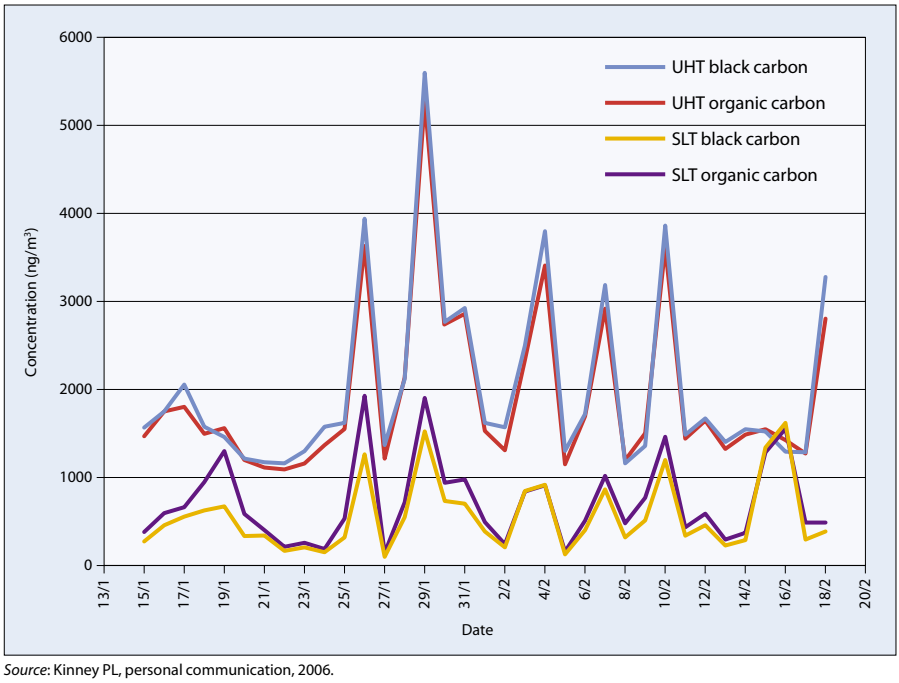
concentrations are likely to occur throughout a city, but the enhancement may be especially pronounced in hot spots where multiple local sources exist. Thus, neighbourhoods that already bear a higher burden of pollution exposure are likely to be further affected during weather-related episodes. This is illustrated by recent unpublished data on black carbon collected in two communities in the New York City metropolitan area that differ in local traffic emission densities and SEP (Fig. 2). The lower-income, urban location has higher average concentrations than the higher-income, suburban location. The two locations respond in similar ways to temporal changes in weather, but the temporal variations (including episodes of unusually high concentrations) are proportionately more pronounced in the lower-income, urban location.

Future research and policy implications

Further research is needed to enable emerging environmental equity data to be incorporated into air pollution guidelines and, possibly, policy action. Essential research projects include those that:

- document whether exposures to and/or health effects associated with air pollution exhibit gradients by demography and SEP in a variety of settings; of particular relevance are studies that would aim at assessing the heterogeneity

Fig. 2. Daily mean black carbon and organic carbon concentrations at an urban high-traffic (UHT) site and a suburban low-traffic (SLT) site in the New York City metropolitan area between 13 January and 20 February 2003



Source: Kinney PL, personal communication, 2006.

of exposure–response functions according to age, gender, health status, educational achievement, income and other related factors, both at individual and at population levels;
- characterize patterns of population exposure resulting from local sources in a variety of settings, especially cities in the developing world;
- frame research questions in a way that is relevant to and responsive to identified needs of policy-makers and affected communities;
- select indicators of SEP that are amenable to policy intervention; and
- involve a range of actors, including representatives of local communities affected by pollution, in problem identification, research design, research practice and translating findings into action to reduce air pollution levels and exposure.

Considerations of environmental equity deserve attention at both national and local levels when developing policies for the control of air pollution sources. At the national level, relevant policy tools include emission limits, air standards and risk assessments. At the local level, there is room for incorporating environmental equity concerns into standards implementation, siting decisions, and transportation and urban planning. Priority should be placed on reducing exposures and risks for populations living, learning and working close to concentrated traffic and other local sources. This could maximize the benefits of risk reduction efforts while also promoting environmental equity.

Policies and programmes related to environmental equity may fall within the purview of several organizations (e.g. agencies charged with protecting health or the environment, as well as those addressing housing, transportation and public welfare/poverty or civil rights). Therefore, authorities and others charged with air quality management may need to establish communications with these diverse actors and affected communities, to coordinate efforts in ensuring environmental equity. This type of coordination is consistent with the principles of the Aarhus Convention under the auspices of the United Nations *(65)*. The identification of environmental inequity does not necessarily imply that a specific policy action is justified. Environmental equity issues will need to be balanced with other societal concerns in reaching policy decisions that maximize health benefits in the context of economic constraints.

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7. Health impact assessment

Bart Ostro

Summary

Health impact assessment (HIA) provides political decision-makers with quantitative and qualitative information about how any policy, programme or project may affect the health of people. In respect of the health consequences of air pollution levels, HIA aims to elucidate current effects or, stated differently, the improvement in health that might be expected through reductions in air pollution.

Worldwide, the overall estimated burden of disease due to outdoor air pollution may account for approximately 1.4% of total mortality, 0.5% of all disability-adjusted life years (DALYs) and 2% of all cardiopulmonary diseases. Certain population subgroups are more affected than others. For example, death is more likely to occur among young children and the elderly. Also, certain regions of the world share a higher burden of disease, such as those heavily dependent on coal for fuel and residents of bigger cities exposed to high concentrations of traffic-related pollution.

To analyse quantitatively the impact on health of outdoor air pollution in a specific city, region or country, information is needed on air pollution concentrations and exposure, the population groups exposed, background incidence of mortality and morbidity, and concentration–response (CR) functions. The choice of which health outcomes to include in the assessment may be determined by the strength of available studies, the accessibility of health information, and the importance of the impact from a health and economic perspective. Most analyses conducted to date indicate that effects on mortality, particularly those relating to long-term exposure to air pollutants, tend to dominate the estimated economic effects.

There are several benefits of conducting HIA. First, specific adverse health outcomes can be quantitatively linked to a given air pollutant and the magnitude of health effects associated with changes in air pollution can be determined. Second, the information can usefully be put towards providing cost-effective improvements in public health. Furthermore, the assessment can identify critical uncertainties and suggest productive areas of research. Quantitative estimates of the impacts of changes in air pollution, even if made with great uncertainty, make the consequences of proposed policies, ▶

- such as the setting of specific ambient air standards or control strategies, more explicit and comprehensible for the public. If economic values are assigned to the health impacts, economic benefits can be determined for alternative air pollution reduction strategies.

Introduction

Over the last decade, hundreds of epidemiological studies have linked exposure to outdoor air pollution with a wide range of adverse health outcomes. These studies have examined the effects of air pollution on morbidity and mortality in the general population. As such, they incorporate effects of air pollution for many different subgroups, activity patterns and exposure conditions. These studies are the basis of several efforts to assess the current effects of air pollution or, stated differently, the improvements in health that might be expected from reducing air pollution. Additional insight into biological mechanisms and subclinical responses are provided by toxicological studies of cells and animals and from studies of humans in controlled exposure chambers. Existing epidemiological studies provide evidence of associations between air pollution concentrations and several adverse health outcomes, including premature mortality, hospital admission for cardiovascular and respiratory diseases, urgent care visits, asthma attacks, acute bronchitis, respiratory symptoms, work loss and restrictions in activity. Thus, HIA, extrapolating the observations from these studies to populations or situations not covered by the studies, can provide estimates of the expected change in the number of cases of premature mortality, hospital admission, etc. that might be expected from a specific change in air pollution.

Many epidemiological studies implicate PM air pollution, a heterogeneous mixture of particles of different size and chemistry, as an important contributor to both morbidity and mortality (see Chapter 10). Significant health impacts of pollution can be expected in urban centres throughout the world, since exposure to PM is ubiquitous. As a result, many HIA have used PM as the marker of pollution. The largest contributor to PM is often fuel combustion from mobile sources (motor vehicles) and stationary sources (e.g. power plants, industrial boilers, factories), but other sources such as road dust and biomass burning may also be significant contributors. Historically, PM has been measured at fixed-site monitors, either as TSP (total suspended particles, which include particles of all sizes), PM_{10} (PM <10 μm in diameter), $PM_{2.5}$ (PM <2.5 μm in diameter) or BS (black smoke, a measure of the darkness of a sample collected on filter paper). Thus the bulk of the epidemiological evidence uses these pollutants as the indicator of exposure. Over the last decade, air pollution standards and regulations have focused more on the smaller particles, because of the evidence that they can penetrate more deeply into the lung. Nevertheless, there is also concern for

other particle sizes such as ultrafine particles (PM <0.1 μm) and certain chemical-specific constituents of PM such as sulfates, transition metals and polycyclic aromatic hydrocarbons. Research continues into the precise particle sizes and chemical constituents that are most responsible for adverse health effects. The existing evidence suggests a likely causal role for $PM_{2.5}$ and its constituents. In addition, $PM_{2.5}$ or PM_{10} serve as reasonable indicators of the general pollution mix that is of concern. Unfortunately, $PM_{2.5}$ has only recently been monitored on a regular basis in some of the industrialized countries, and there is little monitoring of it in other regions.

Previous studies

Health impacts have been assessed for several pollutants, standards and regions. For example, in a recent estimate of the global burden of disease, outdoor air pollution was found to account for approximately 1.4% of total worldwide mortality, 0.5% of DALYs and 2% of all cardiopulmonary disease *(1–3)*. These estimates of total disease burden were based primarily on the effects of long-term exposure to fine particulate air pollution on mortality in adults and of short-term exposure to PM_{10} on mortality in children under five years of age. Because the epidemiological studies suggested that effects on mortality were likely to occur primarily among the elderly, WHO estimated that 81% of the attributable deaths from outdoor air pollution and 49% of the attributable DALYs occurred in people aged 60 years and older. Children under five years of age accounted for 3% of the total attributable deaths from outdoor air pollution and 12% of the attributable DALYs, on the assumption that had the children survived they would have enjoyed a full life expectancy *(2)*. The analysis also indicated that burden of disease in major cities will vary, owing to factors such as the amount of fossil fuel used, weather, underlying disease rates, and population size and density. Burden of disease estimates will be higher in certain regions of the world, such as those heavily dependent on coal for fuel, those with topographical and climatic conditions that limit the dispersion of pollution, and mega-cities with significant concentrations of $PM_{2.5}$ from diesel exhaust, traffic congestion and other fuel combustion sources.

Prior to the global burden of disease study, there were several estimates of the health benefits associated with reducing population exposures to air pollution. Ostro & Chestnut *(4)* generated estimates of the health benefits associated with the proposed standards of the US Environmental Protection Agency (USEPA) for $PM_{2.5}$, while USEPA conducted a regulatory impact analysis to estimate the health and economic impacts of proposed reductions in motor vehicle emissions *(5)*. Kunzli et al. *(6)* estimated the health effects attributed to total and traffic-related PM in three European countries, while Deck et al. *(7)* estimated the health benefits associated with attaining reductions in fine particulate air pollution in two American cities. More recent estimates for Europe have also been developed for 9 cities in Italy *(8)*, 9 French cities *(9)*, 14 Spanish cities *(10)* and 26 cities

in 12 European countries *(11)*. Applying dose–response information, primarily from industrialized countries, the World Bank estimated the benefits of air pollution control in Mexico City *(12)*. Recently, Hubbell et al. *(13)* estimated both the health and economic effects associated with exposure to current levels of ground-level ozone in the United States, while USEPA *(14,15)* estimated the effects associated with meeting alternative ambient standards for fine PM. An assessment was conducted on the health impacts of air pollution and the potential benefits of current and future control strategies in Europe under the Clean Air for Europe (CAFE) programme *(16,17)*. Additional methodological guidance for estimating the health effects of air pollution is provided by Ostro *(18)* as part of WHO's Environmental Burden of Disease project, the USEPA Clean Air Act Compliance Council (an independent scientific review panel for USEPA) *(19)*, the US National Research Council *(20)*, the World Health Organization *(21)* and from Europe, ExternE *(22)* and Sanderson & Hurley *(23)*.

Finally, statistical software to calculate HIA is available (e.g. BenMAP from USEPA and AirQ 2.2.3 from the WHO Regional Office for Europe), although decisions on which epidemiological studies to use and how to apply them are left to the software user. All of these efforts use CR functions culled from the epidemiological literature, relating changes in air pollution measured at fixed site monitors to increases in mortality and morbidity.

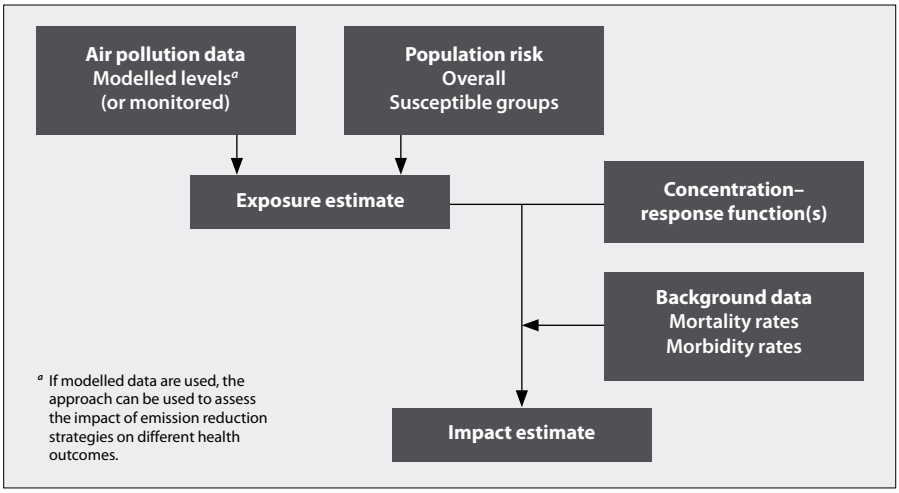
Inputs for the analysis

For a given city, country or region, quantitative assessment of the health impact of outdoor air pollution is based on four components: (*a*) pre- and post-air-pollution concentrations and exposure assessment; (*b*) size and composition of population groups exposed to current levels of air pollution; (*c*) background incidence of mortality and morbidity; and (*d*) CR functions (Fig 1).

Pre- and post-air-pollution concentrations

Analysts need to determine the current exposure of the population to ambient pollution, based either on existing fixed-site monitors or on model-based estimates. Ideally, these concentrations are based on several recent years of complete data (to reduce the influence of an atypical year or season) from monitors that are reasonably representative of population exposure. The monitors should not be unduly influenced by local sources such as a nearby highway, factory or power plant but should rather reflect exposures over a wide area. Typically, fixed-site, population-oriented monitors have been averaged across a metropolitan area to characterize air quality in epidemiological studies. Therefore, a similar metric should be used in HIA. As an alternative to measured pollution concentrations, the global burden of disease project relied on economic models to estimate pollution concentrations for cities throughout the world *(2)*. Besides the current concentration, the analyst needs to determine a counterfactual such as

Fig. 1. Schematic presentation of the main steps of health impact assessment



the background or reference concentration to ultimately determine the change in air pollution being evaluated. The background level is the "natural" concentration of the pollutant that would exist even without any man-made pollution. The reference concentration can be an air pollution standard or goal developed by WHO, USEPA or other governmental institutions. As an alternative, some analysts have simply estimated the impact of some assumed percentage reduction, such as 10–20%, from current levels. Finally, some assessments have calculated the impacts of a specific control strategy, such as the USEPA analysis of motor vehicle standards *(5)*, or are based on the modelled contribution of certain categories of pollution sources. For example, the CAFE analysis estimated the impact of PM from anthropogenic sources *(24)*.

Size and composition of population groups exposed to current levels of air pollution

The relevant population exposed to the change in ambient concentrations is the second data requirement for the assessment. Ideally, these data can be obtained at the local level from census information or other available sources. In addition, since some of the CR functions are specific to certain subgroups (e.g. the elderly, asthmatics, infants and children), baseline demographic data on subgroups would be useful.

Background incidence of mortality and morbidity

Since the epidemiological studies typically estimate relative risk (i.e. the percentage change in health effects per unit of pollution), the third input into the analysis is the underlying incidence of the health effect being estimated (e.g. the underlying mortality rate in the population or deaths per thousand people). Ideally,

these data are available from local surveillance efforts. As an alternative, some analysts have used the baseline rates from the original studies. In this case, additional uncertainty is introduced in applying data from a certain area to another city or country. Misclassification of disease and errors in coding are other potential concerns. When possible, incidence rates should match the age cohort being studied. Finally, analysts should be aware that baseline morbidity and mortality rates will change over time. Changes in the age distribution of the population, health habits or migration can all affect the rates over time. Thus in some cases it is appropriate, at least qualitatively, to indicate the impact that these temporal changes may have on the estimates.

CR functions

The fourth input is a statistical relationship from the epidemiological literature that relates ambient concentrations of pollution to a selected health effect. The quality of the risk assessment depends in part on: (*a*) the accuracy of the CR functions; (*b*) how applicable these functions are to locations and times other than those for which they were originally estimated; (*c*) the extent to which the CR functions apply beyond the range of concentrations for which they were originally estimated; and (*d*) the number of health outcomes specified. Since the selection of CR functions is such an important element in health assessment, this issue is discussed in greater detail below. The available epidemiological evidence concerning health effects from exposure to PM, sulfur dioxide, nitrogen dioxide and ozone is discussed in detail in Chapters 10–13.

Accuracy of the CR functions

The accuracy of the CR functions depends on both the design and quality of the original study (or studies) and how the available studies are chosen for use in the health assessment. The design and quality of the study will affect the accuracy of the results and the completeness of the coverage of the effect. Factors such as the quality of the underlying monitors, the adequacy of the study design, the statistical methods and models used, the accounting for potential confounders, the completeness of the sensitivity analysis and the robustness of the estimates will play a role in the ultimate effect estimates. The decision as to which studies to use will depend on the application of meta-analysis and expert judgement. Some assessments have combined all available studies by weighting each study by the inverse of its standard error or by using other meta techniques, while others have used more subjective judgement to focus on those studies considered to be of highest quality.

Applicability of CR function to different locations

Usually, HIA requires the transfer of CR functions from a given city to other cities in the same country or other countries. The accuracy of this transfer, therefore,

may depend on the similarity of factors such as: (*a*) the composition of the pollutant; (*b*) the spatial associations between individual exposures and concentrations measured at the fixed-site monitors; (*c*) underlying health habits and demographics; and (*d*) exposure to other pollutants, both outdoors and indoors. In the case of PM, depending on the source mix and the local meteorology and atmospheric chemistry, different areas may have differing size distribution and differing chemistry (e.g. proportion of mass consisting of nitrates, sulfates or organics). If toxicity is related to these factors rather than being simply a function of particle mass, additional errors will be introduced by extrapolating the CR functions from one area to another. Second, additional bias in the estimates occurs if the spatial association between the monitor configuration and the associated population is significantly different in the original study than in the applied area. Finally, differences in the CR function could occur if other factors such as poverty, diet, time spent outdoors, use of air conditioning, exercise and work habits, and co-exposure to other pollutants are significantly different between the original and applied locations.

Meta-analyses of earlier mortality studies suggest that, after converting the alternative measures of PM used in the original studies to an equivalent PM_{10} concentration, the effects on mortality are fairly consistent both within and among countries *(25–27)*. The WHO study *(27)* was restricted to European studies only. Overall, the mean estimated change in daily mortality associated with a one-day 10-$\mu g/m^3$ change in PM_{10} implied by these studies is approximately 0.6%, with a range of 0.4–1.6%. A meta-analysis of Asian studies indicated a mean increase in risk of 0.4–0.5% per 10 $\mu g/m^3$ PM_{10} *(28)*. The effect estimates are often larger when researchers have examined the impact of multi-day averages.

In addition to these multi-city investigations and meta-analyses, studies examining the effect on mortality of short-term exposure to PM have been conducted in over 100 separate cities. Reported effect estimates were similar regardless of whether the cities were in Europe, North America or elsewhere, and of whether they were in developed or developing countries. For example, the following effect estimates have been reported for total populations and a 10-$\mu g/m^3$ change in PM_{10} (with 95% confidence intervals): 1.83% (0.9–2.7) for Mexico City *(29)*; 1.1% (0.9–1.4) for Santiago, Chile *(30)*; 0.8% (0.2–1.6) for Inchon, Republic of Korea *(31)*; 1.6% (0.5–2.6) for Brisbane, Australia *(32)*; and 0.95% (0.32–1.6) for Sydney, Australia *(33)*. Mortality estimates associated with PM_{10} or TSP have also been reported for Shenyang, China *(34)*, seven cities in the Republic of Korea *(35)* and New Delhi, India *(36)*. Based on these results, it appears reasonable to apply these estimates to those areas where studies have not been undertaken, since the existing studies were conducted in cities with a range of underlying conditions (e.g. demographics, smoking status, climate, housing stock, occupational exposure, socioeconomic status) and PM concentrations.

Extrapolation of CR functions beyond the observed air quality concentrations

The accuracy of the underlying CR function may be altered by extrapolating the existing function to concentrations either below or above the range of the original study. The current evidence has failed to detect the existence of a threshold at the population level, so calculating effects down to a background concentration is a scientifically supportable assumption. However, some analysts use a conservative approach to extrapolation and only apply the study to a range equal to that of the original study. Others extrapolate the CR functions down to zero, while some have assumed the existence of threshold concentrations below which health effects are unlikely. Regarding the upper range of concentrations, some analysts have extrapolated the CR functions up to the highest observed concentrations in the area under study. The accuracy of these extrapolations depends on the shape of the underlying CR function and is often not observable. Thus an appropriate strategy is to explore the sensitivity of these assumptions on the ultimate result. One issue that is of particular concern is the extrapolation of a linear function to the highest observed concentrations in highly polluted cities or regions. At very high concentrations, it is likely that the CR function will begin to flatten; therefore a linear extrapolation well beyond the range of the underlying data should be carefully evaluated. The global burden of disease project specifically addressed this issue by considering non-linear functional forms and assuming a maximum for the relative risk estimates *(2)*.

Choice of health outcomes

Often, the analyst must choose to focus on a subset of several health end-points that have been studied. The choice of which end-points to include in the quantitative assessment may be determined by the strength of available evidence from the epidemiological as well as other scientific literature, the accuracy of the definition of the end-point under consideration, the availability of information on baseline rates, and the importance of the impact from both the health and, perhaps, the economic viewpoint. It is much easier to choose a given end-point to include if many studies of this health effect exist, particularly if the studies involve a wide range of cities, seasonal patterns, meteorology, co-pollutants and background health status. The daily time series studies of mortality and PM provide a good example of this, in that they have been conducted in five continents and show reasonably consistent results. In addition, all-cause mortality has a clear and consistent definition (as opposed to, for example, asthma or mortality from cardiovascular disease) regardless of location. Finally, most of the analyses to date indicate that effects on mortality, particularly those relating to long-term exposure to air pollution, tend to dominate the economic effects, often accounting for 80% or more of the total.

The consistency of the daily time series studies among so many locations suggests it is reasonable to extrapolate the findings of the effects of long-term

exposure to other areas. Most of the current evidence on long-term exposure is based on a few cohort studies in the United States, using $PM_{2.5}$ and sulfates as exposure metrics *(37–39)*. These cohort studies follow large populations over several years so that, after controlling for other factors that affect longevity, such as smoking and body mass index, the impact of air pollution can be determined. It is important to include these long-term estimates, developed from cohort studies, in any HIA of air pollution since the daily time series studies will, in general, significantly underestimate the effects of air pollution *(20)*. Both the attributable number of cases of premature mortality and the effects on average lifespan or "years of life lost" will be underestimated. Existing estimates from the cohort studies suggest an effect that is several times greater than that provided by the time series studies. The relative risk estimates obtained from the cohort studies can be applied to population life tables to derive estimates of average reduction in lifespan associated with air pollution *(21,40)*. Cohen et al. *(3)* applied these coefficients obtained in the United States to widely different regions throughout the world in order to calculate the global burden of disease attributable to outdoor air pollution.

Benefits of conducting impact assessment

Identification of the type and magnitude of health effects associated with changes in air pollution.

In quantifying the expected health effects associated with changes in air pollution, the impact assessment explicitly documents the types of adverse health outcome (e.g. premature mortality, asthma attacks, work loss) that can be quantitatively linked to a given air pollutant and also provides a broad estimate of the magnitude of each outcome.

Identification of uncertainties and the value of information

As part of the process, the assessment can identify critical uncertainties, suggest productive areas of research and assess the value of information. For example, in assessing the impact of motor vehicle emissions standards, USEPA *(5)* estimated both the health and economic effects of the changes in ozone and PM that would result from changes in oxides of nitrogen. The analysis identified several factors that had a significant impact on the results. One major factor that dominated the impact assessment was the application of two studies that linked long-term exposure to $PM_{2.5}$ to premature mortality *(37,41)*. Other important factors identified included risk estimates of the effects of long-term exposure on mortality hazards (age-specific death rates), the economic valuation of reductions in mortality risk, assumptions about thresholds, and assumptions about the time lag between reductions in pollution and subsequent changes in mortality. As a result, additional sensitivity analyses were conducted using alternative assumptions about these

factors to indicate the subsequent impact on the overall results. Also, as a result of this and other regulatory impact analyses, USEPA began to focus additional research efforts on new cohort studies that would examine the effects of long-term exposure to PM (see Chapter 10). In addition, funds were provided for a reanalysis of studies linking long-term exposure to premature mortality *(38)*.

Making implicit information explicit

In many cases, decision-makers for ambient standards or control strategies have some presumption about the expected benefits of their decisions. The expected benefits are often an implicit part of calculus leading to the final decision, but may remain unknown to other government officials, the regulated industries and the public at large. Quantitative estimates of the impacts of changes in air pollution, even if made with great uncertainty, render this information more explicit, thereby allowing for public information and scrutiny.

Providing an input in calculating economic benefits

If economic values are assigned to the expected health impacts, a full accounting of the economic benefits can occur. This information can be used to help prioritize the actions regarding air pollution control relative to other public health interventions. It may also serve to help set priorities among alternative strategies that reduce air pollution levels. Finally, if cost information is provided, formal cost–benefit analysis can be conducted, if desired.

Providing information for standard setting and regulation

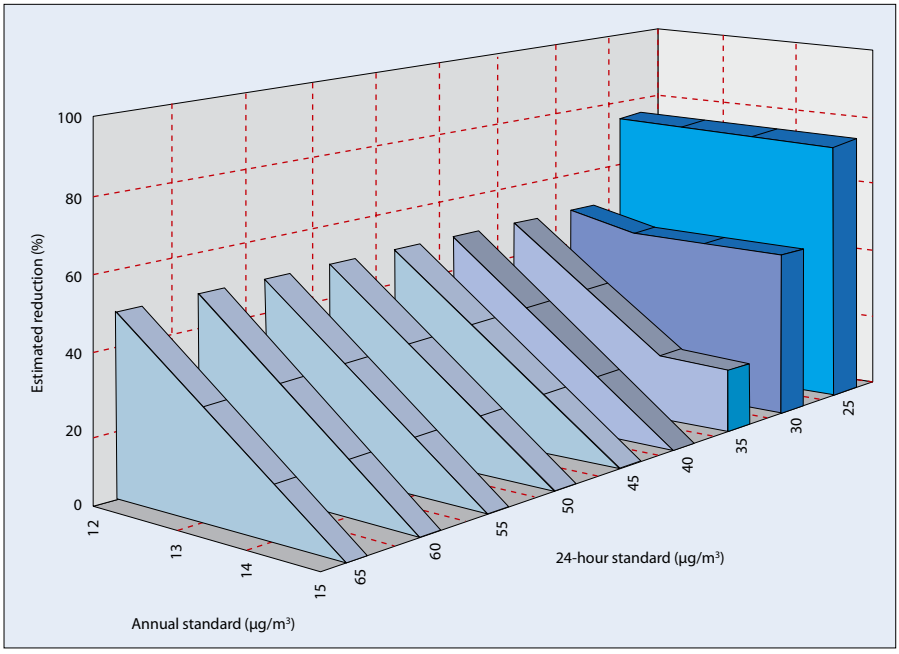
Assessment of health benefits can be an important tool in decision-making. Perhaps the best example of HIA playing a major role in regulation is the reduction of the lead content of petrol in the United States. The USEPA analysis of the lead content of petrol calculated the direct benefits to health of reducing lead in the environment, in terms of reduced neurodevelopmental effects as measured by IQ and in terms of cardiovascular effects, including changes in blood pressure and subsequent risk of cardiovascular disease *(42)*. The analysis also examined indirect health benefits such as those associated with reduced misfuelling (using leaded petrol in vehicles that require unleaded fuel). Misfuelling disables catalytic converters, leading to an increase in pollutants such as nitrogen dioxide and hydrocarbons. The analysis demonstrated that, despite the significant costs to refineries, the health and economic benefits from reducing the lead content would far outweigh the costs.

In a recent case, USEPA used impact assessment to evaluate the effect on mortality of alternative national ambient air quality standards for PM. Specifically, USEPA staff calculated the extent to which different concentrations and averaging times for $PM_{2.5}$ are likely to reduce the estimated risks of mortality attributed to long-term exposure to $PM_{2.5}$ *(14)*. Staff applied results from the extended study

of the American Cancer Society cohort *(39)*, in which effects were estimated down to 7.5 μg/m^3, the lowest observed level in the study (although, as mentioned above, some other efforts have estimated effects down to the background concentration of $PM_{2.5}$, which is assumed to be between 2.5 μg/m^3 and 5 μg/m^3). In addition, thresholds other than 7.5 μg/m^3 were examined.

Using air quality data from 2001–2003, five cities were used as examples to estimate the percentage reductions in mortality attributed to $PM_{2.5}$ as long-term exposure moves from the current USEPA $PM_{2.5}$ standards (15 μg/m^3 annual average and 65 μg/m^3 24-hour average, based on the three-year average of the 98th percentile of 24-hour $PM_{2.5}$ concentrations) to various alternative concentrations. The alternatives examined range from 12 μg/m^3 to 15 μg/m^3 as an annual average and from 25 μg/m^3 to 65 μg/m^3 as a 24-hour average. The analysis also examined the impact of allowing a different number of exceedances (i.e. using a 99th or 98th percentile) of the 24-hour average. Fig. 2 summarizes the results for Los Angeles *(15)*. The assessment first demonstrates that moving from current standards to an annual average of 7.5 μg/m^3 would result in a saving, in the steady state, of approximately 1500 premature deaths per year, with a 95% confidence

Fig. 2. Estimated percentage reduction in $PM_{2.5}$-related long-term mortality risk in Los Angeles for alternative annual and 24-hour average standards relative to the current USEPA standard



Note. Estimates based on Pope et al. *(39)* for alternative standards (24-hour standard is based on 98th percentile) using baseline of mortality associated with current standards. Estimate of 1500 represents residual mortality from air pollution after meeting current USEPA standards of 15 μg/m^3 annual average and 65 μg/m^3 24-hour average. Assumed hypothetical threshold equals lowest measured level of 7.5 μg/m^3. The vertical axis represents percentage age reduction from the baseline of 1500.

Source: US Environmental Protection Agency *(15)*.

interval of 530–2600. Next, as represented by the first triangle in Fig. 2, with a 24-hour standard of 65 μg/m^3, alternative annual average standards of 15 μg/m^3 down to 12 μg/m^3 would reduce mortality from 0% to 50%, respectively. The following triangles show that lowering the 24-hour average standard from 65 μg/ m^3 to 40 μg/m^3 has no additional benefit in terms of reductions. This suggests that the annual average standards of 15 μg/m^3 and below are more stringent in Los Angeles than a 24-hour standard as low as 40 μg/m^3. However, a 24-hour standard of 35 μg/m^3 does bring additional reductions in mortality of roughly 15%. Moving to a 24-hour standard of 30 μg/m^3 results in a 45% reduction, while a 24-hour average standard of 25 μg/m^3 results in a 74% reduction in mortality from baseline, independent of the annual average (i.e. at this point, the 24-hour standard is more stringent than any of the proposed annual average standards). Thus this impact assessment, based on the effects of long-term exposure to $PM_{2.5}$ on mortality, indicates the magnitude of the resulting reductions in mortality and the relative effects of different combinations of annual and 24-hour average standards.

A simple example of the methodology

To demonstrate the methodology for estimating the effects of outdoor air pollution, we use data from Bangkok, Thailand. Bangkok, a warm and humid city, is situated on a relatively flat plain and has a population of approximately six million (with up to ten million in the metropolitan area). Because of the relatively low proportion of roads to surface area, the city has difficulty supporting the large number of cars (approximately four million) and motorcycles used in the city, many of which have little or no pollution control. The ubiquitous traffic jams contribute a large share of the PM_{10} coming from incomplete combustion of fossil fuels used by the transportation sector. In this example, we calculate the expected number of premature deaths due to short-term exposure to PM_{10}. Additional details regarding the methodology can be found in Ostro *(18)*.

To calculate the expected number of deaths due to air pollution (E), we take the product of:

$$E = beta \times B \times P \times C$$

where:

E = **expected number of premature deaths due to short-term exposure**
beta = **percentage change in mortality per 10-μg/m^3 change in PM_{10}**
B = **incidence of the given health effect (deaths per 1000 people)**
P = **relevant exposed population for the health effect**
C = **change in PM_{10} concentration (μg/m^3 × 0.1).**

Our estimates for the annual average PM_{10} were derived from continuous measurements taken between 1996 and 2001 from seven monitors throughout the

metropolitan area. The annual average for PM_{10} for the six years of data was 70.28 μg/m^3. As a reference concentration, we use an assumed background concentration of 10 μg/m^3 PM_{10}. We also examined a reference concentration equal to the new air quality guideline level of 20 μg/m^3 PM_{10} (see Chapter 10). Mortality data from the Thai Ministry of Health for 1998–2001 were used to determine the existing baseline mortality rate of 0.00558. We assumed a total population of six million, based on data from the Ministry. As discussed above, a reasonable range for beta is approximately 0.6%, with a range of 0.4–1.6%. Thus, we expect a daily increase in mortality of 0.6% for each 10-μg/m^3 change in PM_{10}. As an alternative, we could use the beta derived from a mortality study in Bangkok of 1.7% (95% CI = 1.1–2.3) *(43)* or some combination of the Bangkok and global estimates. Thus, we obtain:

E = (0.006) (0.00558) (6 000 000) (70.28–10)(0.1) = 1211.

Therefore, the impact of the current ambient level of PM_{10} (70.28 μg/m^3), relative to a background concentration of 10 μg/m^3, is approximately 1200 premature deaths per year with a 95% CI of 807–3229. If we assume a reference concentration of 20 μg/m^3 $PM_{10,}$ the mean estimate becomes 1010 premature deaths.

The estimation presented above does not consider the impact of long-term exposure or any morbidity impacts, and therefore presents only a part of the total impact of pollution on health in Bangkok. Assuming that the mortality for those aged >30 years increases by a rate of about 0.6% per μg/m^3 of long-term $PM_{2.5}$ concentration *(39)* and assuming that $PM_{2.5}$ = 0.6 PM_{10} in Bangkok, the current PM levels in Bangkok (0.6 × 70 μg/m^3 = 42 μg/m^3 $PM_{2.5}$) are associated with increase of mortality risk when compared with the air quality guideline level (10 μg/m^3 $PM_{2.5}$) by a factor of:

(42–10) × 0.6% = 19.2%.

For the population of Bangkok (approximately three million adults), the annual number of adult deaths is 49 560. Thus the annual number of deaths attributable to long-term exposure to $PM_{2.5}$ is 49 560 × 0.192, or 9416. Even compared to the interim target 2 (IT2) of the PM air quality guidelines (25 μg/m^3 $PM_{2.5}$), the mortality is increased by:

(42–25) × 0.6% = 10.2%.

This means that long-term $PM_{2.5}$ in excess of IT2 can be linked to an increase of 5055 in the annual number of deaths in Bangkok. Achieving IT2 would, in the long term, halve the mortality toll caused by PM exceeding the guideline level. These estimates assume that the results of Pope et al. *(39)* can be linearly extrapolated to the higher exposures in Bangkok. However, at some pollution level, the CR function may become less than linear. A discussion of the application of nonlinear functions can be found in Ostro *(18)*.

Uncertainties

Clearly, there are many uncertainties involved in estimating the health effects associated with outdoor air pollution. Over time, some of these will be reduced as new research is conducted. Nevertheless, some uncertainty will be inherent in any estimate. For many of these issues, the bias could be either positive or negative. We briefly discuss below some of the major uncertainties.

There are several uncertainties and limitations involved in using epidemiological evidence for quantitative assessment. A key assumption is that the relationship between air pollution and health effects is causal. Then, the observed association can reasonably be used to predict how changes in pollution concentrations will influence the incidence of health effects. Observational epidemiological studies are able to demonstrate whether an association exists between health effects and pollution concentrations, but it is more difficult for the studies to prove that the relationship is causal. It is possible that a statistically significant relationship is actually due to some unidentified factor that is correlated with pollution concentrations. Nevertheless, the likelihood of causation is strengthened when: (*a*) epidemiological results are replicated by similar findings in different studies with variable underlying conditions; (*b*) multiple health outcomes appear to be affected in a consistent and coherent manner; and (*c*) the results are supported by either toxicological or controlled studies on humans. Such is the case with PM, where numerous studies have found a similar magnitude of effect for mortality, and have also linked it with a wide spectrum of cardiorespiratory health outcomes. There is a growing body of laboratory and clinical evidence regarding the health effects associated with exposure to PM, although biological mechanisms that underlie the observed epidemiological associations have not been fully elucidated. This adds some additional uncertainty when using epidemiological relationships to predict how health may change as a result of changes in ambient pollution concentrations.

Another large uncertainly concerns dependence on epidemiological studies for risk estimates. Epidemiological studies have both advantages and disadvantages in estimating the health impact of air pollution. Epidemiological studies involve the study of humans in real situations, and thus human health effects are observed under a wide range of behavioural situations and conditions. The obvious advantage of such studies is the lack of a need to extrapolate results across species or dose levels. A wide range of health outcomes can be studied, including mortality, and a wide range of subgroups can be examined in detail. For example, it is possible to examine the effects of air pollution on individuals with severe asthma or on elderly people with chronic bronchitis. In addition, researchers can examine a wide range of pollutants and pollutant mixes by considering multiple seasons or locations, and exposures over many days, months and years can be investigated.

Among the disadvantages of this approach are imprecision in measuring exposure and response, and potential confounding of the air pollutant measure by

other covariates. For example, exposures are typically based on existing fixed-site monitors. Thus, there will be question about how well these measurements represent actual exposure. In addition, some endpoints such as hospital admissions, emergency department visits and asthma attacks involve subjective evaluation of severity. Covariates that may confound the association between air pollution and health, such as seasonality and co-pollutants, have been an important area of inquiry and analysis *(44)*. Also, it is difficult for epidemiological studies to determine the underlying biological mechanism of the effects of air pollution. Some recent studies examining various measures of cardiac function, however, are providing important insights into mechanisms. Finding a statistically significant association between a health effect and a specific air pollutant does not prove causality. The inference of causation is strengthened, however, if epidemiological results are duplicated across several studies and if a range of effects is found for a given pollutant.

There may also be uncertainty about possible non-linearity or thresholds in the CR functions. It remains uncertain whether there is a threshold concentration below which health effects no longer occur, or whether the slope of the CR function changes significantly at lower concentrations. Available epidemiological studies have not usually addressed the question of thresholds, and epidemiological data are not always sufficient for making such a determination. Nevertheless, most recent epidemiological studies show statistically significant and relatively linear associations between PM concentrations and health end-points over the full range of concentrations, with no evidence of a threshold at the population level. A log-linear function is more plausible and should be used to generate effect estimates for cities with very high concentrations of pollution. For both short- and long-term exposures, one can apply a threshold to determine the impact on the overall estimates. Assumptions about the shape of the CR function, and the acceptability of extrapolating the results from one region to another, are probably the major sources of uncertainty in HIA.

An additional uncertainty involves co-pollutants. It is likely that some of the estimated health effects include the effects of both PM and other correlated pollutants. Since many of the pollutants come from a common source (e.g. fuel combustion), the use of PM as an index for the mix of pollutants is reasonable but conservative. Exposure to other pollutants that are not related spatially or temporally with PM has demonstrable health effects that are not included in our estimates.

Another source of uncertainty derives from the fact that estimates are provided for only a subset of adverse outcomes, owing to lack of available data. For example, some HIAs do not include the effects of air pollution (including PM) on asthma and hospital admissions because of the lack of baseline prevalence rates in the region under study. In addition, many of the original studies are restricted to certain age groups or levels of severity. For example, hospital admission studies

in the United States are often restricted to those over the age of 65, and many asthma studies focus on asthmatics with relatively severe current asthma.

Finally, there is uncertainty concerning the baseline rates of the considered health outcome in the studied population. Often, one will have to assume a baseline incidence level for the city or country of interest. In addition, the incidence will change over time as health habits, income and other factors change.

Ultimately, there are several methods for expressing the underlying uncertainty in HIA estimates. The level and range of uncertainty can be expressed descriptively and qualitatively through the use of confidence intervals, through sensitivity analysis of the more important assumptions and through the use of expert judgement and subjective probability exercises.

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8. Application of guidelines in policy formulation

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Summary

The WHO air quality guidelines aim to provide a uniform scientific basis for understanding the effects of air pollution on human health. Using these guidelines as a basis, local or national air quality standards can be developed for the management of air quality.

This chapter addresses some key issues that need to be considered in order to move from guidelines to air quality standards and management. In addition to the technical aspects, there are political, economic and social considerations. Technical experts can play an important role in informing policy-makers on the relevant scientific findings that can help in defining standard levels and mitigation measures. Nevertheless, when making final decisions on air quality standards, policy-makers must still make informed decisions on choosing the air pollutants to regulate, defining adverse health effects, sensitive populations, acceptable risk levels, how to deal with uncertainty, and the role of costs.

The implementation of air quality standards requires specification of monitoring and reporting techniques and compliance criteria. Mitigation measures should be based on careful analysis of their potential for complying with standards, as well as their costs and benefits. To be effective, standards should be established with explicit enforcement measures and communication strategies.

Finally, recognizing the nature of air pollution risks and the fact that no truly safe level of exposure has been found for several pollutants, continual minimization of population exposures and improvements in air quality are recommended.

Introduction

The main purpose of air quality management is to protect public health and the environment from the adverse effects of air pollution. Adequate air quality management strategies encompass many activities, including risk assessment, air quality and emission standard setting, monitoring and enforcement, implementation of control measures, and risk communication. The use of air quality standards, however, has become the cornerstone of air quality management, whose

role, adopted and enforced by regulatory authorities, is to define the level of acceptable air pollution for a country or region.

The primary aim of the guidelines presented here is to provide a uniform basis for protecting public health from the effects of air pollution. However, these guidelines have the character of recommendations, and it is not intended or suggested that they simply be adopted as standards. As presented in Part 2, the epidemiological evidence indicates that the possibility of adverse effects remains even if the guideline value is achieved, and some countries may select even lower levels for their standards. This chapter discusses some of the factors that should be evaluated when moving from guidelines to standard setting and policy formulation.

In addition to the pathophysiological basis for the adverse effects that may be associated with exposure to air pollution, these factors include current exposure levels and risk perceptions of a given population, and, of equal importance, the specific social, economic and cultural conditions encountered in a given location. Provisions designed to protect vulnerable groups, such as young children or the elderly, can also influence the stringency of air quality standards. In addition, the standard-setting procedure may be influenced by the feasibility and costs of implementing and enforcing the standards. These considerations may lead to a standard above or below the respective recommended guideline value *(1)*, as can be observed from the air quality standards of countries around the world included in Table 1.

Setting air quality standards

Air quality standards are considered to be the acceptable levels of air pollution, in terms of potential impacts on public health and the environment, that are

Table 1. Selected air quality guidelines and standards

Source	Sulfur dioxide (µg/m³)			
	1 year	24 hours	1 hour	10 minutes
WHO *(2)*		20		500
European Union *(3)*		125	350	
United States *(4)*	78	366		
California *(5)*		105 [c]	655	
Japan *(6)*		105	262	
Brazil *(7)*	80	365		
Mexico *(8)*	78	341		
South Africa *(9)*	50	125		500
India *(10)* (sensitive populations/residential/industrial)	15/60/80	30/80/120		
China *(11)* (Classes I/II/III) [d]	20/60/100	50/150/250	150/500/700	

[a] Not to be exceeded more than 3 days per year.
[b] Not to be exceeded more than 35 days per year.
[c] Photochemical oxidants.
[d] Class I: tourist, historical and conservation areas; Class II: residential urban and rural areas; Class III: industrial and heavy traffic areas.

adopted by a regulatory authority as enforceable. Countries have adopted different names for such goals. In China, India and the United States, for instance, they are called the national ambient air quality standards *(4,10,11)*, whereas in Canada and the EU they are referred to as limit values *(12)*. For consistency, we will refer to such goals throughout as air quality standards. In addition to the concentration level and the averaging time established by these guidelines, air quality standards are regulatory instruments that also specify how to monitor, evaluate and comply with the goals.

When setting air quality standards, decision-makers will be faced with some of the following questions.

- Which pollutants and pollutant properties should be regulated?
- Which adverse health effects should the population be protected from?
- Who should be protected from these effects?
- What level of risk is acceptable to the population?
- How will uncertainty in the evidence affect the decision-making process?
- How feasible will it be to comply with the proposed standards, and at what cost?

Selection of pollutants and pollutant characteristics to regulate

The air we breathe is made up of hundreds of chemicals, many of which are a direct result of human activity. The first steps in defining what to regulate are to evaluate the air pollution problem and to carry out a thorough review of research on the potential hazards of such pollutants to human health and the environment. This process draws on evidence from a wide variety of toxicological and epidemiological studies linking exposure to air pollutants to their potential effects.

Nitrogen dioxide (µg/m³)			PM_{10} (µg/m³)		$PM_{2.5}$ (µg/m³)		Ozone (µg/m³)	
1 year	24 hours	1 hour	1 year	24 hours	1 year	24 hours	8 hours	1 hour
40		200	20	50 [a]	10	25 [a]	100	
40		200	40	50 [b]			120	
100			50	150	15	65	157	
		470 [c]	20	50	12	65	137	180 [c]
	113			100				118 [c]
100		320	50	150				160
		395	50	120	15	65	157 [c]	216
94	188	376	60	180				235
15/60/80	30/80/120		50/60/120					
40/40/80	80/80/120	120/120/240	40/100/150	50/150/250				120/160/200

Combining this evidence, researchers and regulators can identify potentially hazardous pollutants. These guidelines provide a review of the international scientific literature and evidence that can be used in setting standards. Nevertheless, in determining effects and levels for standard setting, local studies should be taken into consideration when available since population responses to air pollution may vary owing to differences in population health, lifestyle characteristics, exposure patterns and pollutant mixes.

Once a pollutant is considered hazardous because of its potential effects on human health and the environment, information on the current levels and exposures to such pollutants should be obtained to determine the scale of the problem. Evaluation of health impacts, as described in Chapter 7, is a useful tool that can be used to determine the magnitude of the air pollution risks faced by the population.

The determination of pollutant characteristics to regulate depends on the nature of population exposure and response patterns. Standards differ in their averaging times, depending on the health outcomes they are trying to prevent, from 1-hour maximums to 8-hour or 24-hour means to annual averages, depending on the evidence of exposure duration that is linked to the adverse health effect. Short averaging times are created for protection from peak concentrations, with acute population exposures and health effects, whereas longer averaging times are suited to protecting the population from chronic exposures and their consequent long-term and mostly irreversible health outcomes. For instance, the PM guidelines presented here were established to protect populations from both short-term (24-hour guidelines) and long-term exposures (annual guidelines), since effects have been identified for both acute and chronic exposure windows for this pollutant.

The pollutant characteristics to be regulated must also be considered when reviewing the scientific literature and setting standards. This issue has arisen mostly from the regulation of PM. PM was originally regulated as total suspended particles, including particles with diameters up to 100 μm. As the evidence grew, standards shifted to regulate smaller particles – first PM_{10} and then $PM_{2.5}$ – as scientists found that the smaller particles are those that exert greater effects on human health. Currently, the scientific debate is whether agencies should measure and regulate even smaller particles, such as $PM_{1.0}$. While mass concentration, reported as $\mu g/m^3$, has been the regulated and most studied indicator of PM, other characteristics are appearing to be increasingly important. More recent scientific evidence has shown that the toxicity of particles is related not only to their size but also to their physical and chemical properties, including particle number, shape, composition and reactivity (see Chapter 10). These issues are considered when the guidelines are formulated and their conclusions, based on a review of the accumulated scientific evidence, determine the pollution indicator(s) to be considered when setting standards.

Adverse health effects

Exposure to different air pollutants has been linked to a wide variety of health outcomes, from acute symptoms to chronic disease and death. These outcomes can be characterized by their magnitude, duration and reversibility. In setting air quality standards, the health effects that the population is to be protected from need to be defined in order to identify the research to review and the relevant findings to incorporate into the standard-setting process. The distinction between adverse and non-adverse effects, however, poses considerable difficulties. As decision-makers consider effects that are temporary and reversible, or involve biochemical or functional changes whose clinical significance is uncertain, judgements must be made as to which of these less serious effects should be considered adverse *(1)*.

For instance, during the review of the ozone standards in the United States, significant debate arose in the assessment of evidence on the relationship between ozone exposure and transient, apparently reversible effects such as lung capacity, flow resistance and epithelial permeability and reactivity *(13)*. The way in which such evidence is used, therefore, often includes a certain degree of subjectivity and uncertainty. It is important to be explicit about such judgements, in order to open up the debate and make the decision-making process more transparent.

It should be noted that, because of different cultural values and health situations, attitudes towards adversity and risk perception may differ within different sections of a population and between countries *(1)*. Social science researchers have long identified cultural values as key factors in determining people's perceptions of risk. Research in the United States, for instance, has identified the "white male effect", whereby Caucasian men systematically perceive risks to be lower than those perceived by women and members of other ethnic groups. Experts have attributed much of this effect to differences in cultural values and views of the world *(14)*. Therefore, where cultural values differ, perceptions of air pollution risk may vary even when similar air quality is experienced.

Acceptability of risk

In the absence of clearly identified thresholds, the adoption of air quality standards inevitably assumes that a certain level of risk is acceptable to the population. For most air pollutants, no "safe" levels have been found whereby no health effects are observed following exposure. In fact, for many pollutants, adverse effects have been associated with low, almost background levels of exposure *(15,16)*. Since the process of setting air quality guidelines and standards aims at defining levels that do not pose adverse effects on health, how can such levels be determined when the scientific evidence indicates that no thresholds exist? The exercise in defining air quality standards requires informed judgement by decision-makers on the level of acceptable risk to the population. The degree of acceptability of risk may vary between countries because of differences in social norms and values, the

severity of the air pollution problem, the degree of risk adversity, and perceptions among the general population and various stakeholders.

The setting of air quality guidelines and standards under such circumstances, where no clear "safe" levels of exposure exist, intrinsically involves risk management and the definition of acceptable risk to a population. In setting standards, decision-makers can evaluate the risks posed to their constituency at different air pollution levels by conducting a formal health impact assessment, as discussed in Chapter 7. They thereby explicitly determine the acceptable level of risk for their populations, given the specific circumstances. In an attempt to help countries evaluate air pollution risks and to allow them to make their own judgements about acceptable levels of risk, the second edition of *Air quality guidelines for Europe (17)* provide only the value of the concentration–response function for PM and mortality, instead of setting specific guideline levels. This was perceived as not very practical or feasible for developing countries, which may not have the necessary resources to conduct health impact assessments and prefer to receive clear guidance from WHO in setting their air quality standards.

The typical message being sent to the population is that compliance with air quality standards implies that little or no risk is being posed to their health and therefore it is not necessary to reduce pollution below standard levels. This, however, is not the case for some pollutants, and significant risks have been demonstrated even below standard levels. Given the nature of air pollution risks and the lack of clear thresholds, several countries have chosen to shift their air quality management paradigms to include risk reduction or minimization measures. Canada has adopted such a model with the "continuous improvement" provision as part of *Canada-wide standards for particulate matter (PM) and ozone (18)*. This acknowledges that some areas, while meeting air quality standards, still experience air pollution levels that pose risks to human health. The provision encourages such jurisdictions "to take remedial and preventative actions to reduce emissions from anthropogenic sources". The European Commission has proposed new EU air quality standards that would entail risk reduction paradigms as part of the "exposure reduction" targets for $PM_{2.5}$ *(12)*, wherein Member States should reduce levels of $PM_{2.5}$ by 20%[1] of 2010 values by the year 2020. These new air quality management models send a clear message that simply meeting current air quality standards is not enough, and that the goals of air quality management should be to reduce and minimize risk.

Vulnerable population groups

Additional judgements are necessary in the standard-setting process when defining whom the standards are intended to protect. While it is commonly agreed

[1] That is, 20% of the "average exposure indicator", which is the three-year average of urban background concentrations; 2010 corresponds to 2008–2010 and 2020 corresponds to 2018–2020.

that air quality standards should protect the general population, some governments have clearly stated that standards should also protect sensitive or vulnerable population groups. Sensitive population groups are those whose health status or specific characteristics (such as the developmental phase in children, reproductive age in women, pre-existing disease in some individuals, or reduction of reserve capacity in the elderly) make them especially likely to experience adverse health effects following exposure to pollutants. Chapter 5 discusses the determinants of susceptibility in greater detail.

Population groups who experience elevated risks owing to the magnitude of their exposures are also considered vulnerable *(17)*. These include healthy people performing vigorous outdoor activities, such as athletes or construction workers, and those who live or work near major sources such as busy roads or industries. The guidelines presented here are recommended to apply to all environments where population exposure occurs[2] and therefore protect all population groups. Air quality standards that are differentiated by land use (such as in China and India, where air quality standards for industrial areas are up to 100% and 250% higher than for residential areas, respectively) *(10,11)* are not recommended, since many countries do not strictly enforce zoning laws so that people often live in or near industrial zones. Such practices can lead to heightened environmental inequity, especially for the poor populations that tend to reside in these "non-residential" zones.

Since a wide variety of vulnerable population groups exists, it is up to decision-makers to evaluate the evidence and decide who should be protected by air quality standards. Special consideration should be given to determining appropriate levels in order to protect these vulnerable groups. This may be done by evaluating studies that have specifically looked at the response of such populations to pollutant exposures, or through a conservative review and interpretation of the evidence to ensure adequate protection of vulnerable populations.

Uncertainty

Many uncertainties exist in the process of standard setting related to the strength of the scientific evidence on the relationship between exposure and response. Uncertainty is inherent in science, and thus decisions that involve scientific issues such as the environment and health must be made using the best information available. Thus, it is up to the decision-maker, with the help of technical experts, to evaluate the evidence and uncertainties involved and make appropriate judgements.

In evaluating the scientific literature, there may be insufficient information about the impacts of pollutants, the population at risk and the magnitude of the effect. In addition, results from existing studies may contradict each other, and

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[2] Except for occupational settings, because of potential differences in population susceptibility of the adult workforce in comparison with the general population.

be inconsistent in their findings. Even where information exists, and studies associating exposure to a certain health effect are consistent, uncertainty may still remain about the mechanism of such effects.

In addition to the many uncertainties related to the scientific evidence, the process of extrapolating results from the study population to other populations, as is commonplace in developing countries where few local studies are available, raises questions as to the validity of generalizing study results. Air pollution may yield different magnitudes of an effect in different settings owing to a suite of environmental and population factors. Environmental factors could include the levels, composition, mixes and distribution patterns of pollutants, all of which may be different in the local setting compared to those of the studies used in establishing guidelines or standards. Population and lifestyle characteristics that may modify effects include age structure, health care systems, activity patterns, home and building structures, disease patterns and baseline health, which can alter the susceptibility and pollution exposure patterns of the population.

Uncertainty can inhibit the policy-making process when decision-makers do not have enough evidence to make informed decisions. Often, the regulated community will advocate delaying regulations until further research is conducted or uncertainty is reduced. Nevertheless, it is important for technical experts to explicitly present policy-makers with the uncertainty in the evidence, so that transparent decisions can be made by evaluating both the evidence and the uncertainty in the evidence.

Where there is uncertainty, decision-makers are faced with either acting immediately, and possibly implementing inefficient policies, or waiting until further information becomes available while exposing their constituents to serious risks *(19)*. Both acting and waiting can have serious and irreversible consequences. The mere presence of uncertainty does not necessarily warrant delaying regulation, however, as scientific uncertainty will always exist and may never be completely resolved. Thus the precautionary approach is often used, so that cost-effective measures are not delayed by a lack of scientific certainty when serious threats to the environment and human health exist *(20)*.

Feasibility and cost considerations

The feasibility and costs of complying with proposed air quality standards can often be critical factors in the decision-making process. The feasibility of complying with standards depends on the current levels and sources of pollution, the options available for reducing emissions, and information on how emission reductions will affect ambient concentrations. The political environment is also a key factor in setting and implementing standards, and political will can often determine the passing and stringency of standards.

Countries should evaluate current pollution levels and determine how far removed from these guidelines or proposed standards they are. If current ambient

concentrations are far removed from proposed levels, adoption of these guidelines could be seen as a long-term objective. Countries can move towards these guidelines gradually by adopting the interim targets proposed here as they begin to reduce ambient air pollution. The interim targets are intended as incremental steps in a progressive reduction of air pollution in more polluted areas; they are intended to promote a shift from concentrations involving acute, serious health consequences to concentrations that, if achieved, would result in significant reductions in the risk of acute and chronic effects. Such progress towards *guideline values* should be the objective of air quality management and health risk reduction in all areas.

In determining how emissions and, consequently, ambient levels can be reduced, it is also necessary to define the nature of the pollution sources. Information from emission inventories and dispersion models are critical in air quality management, in order to understand where pollutants come from and how their control will affect air quality. Because of the potential for long-range transport of pollutants or their precursors it is possible that, even with stringent control measures, compliance with air quality standards would be unachievable; thus a regional or international approach may be needed in some circumstances.

While some countries explicitly prohibit the evaluation of compliance costs in favour of basing standards solely on public health criteria, others require it. Costs, explicit or implicit, are always a consideration for decision-makers faced with difficult trade-offs among important values such as health, safety, mobility and education when allocating scarce resources to social programmes. For countries that are just beginning to control air pollution, and where levels greatly exceed proposed standards, relatively simple and inexpensive controls can achieve significant improvements. In contrast, it becomes harder and harder to reduce marginal amounts of air pollution as air quality improves, and new mitigation measures cost significantly more.

Cost–benefit analysis can play an important role in informing decision-makers about the associated costs and benefits of complying with standards. When a cost–benefit analysis is initiated, debate will often arise on how to quantify the benefits from air pollution mitigation. Economists have made many advances, however, in refining methodologies to value human health and estimate people's willingness to pay to avoid illness and death, thereby allowing policy-makers to directly compare the costs and benefits of regulation. Uncertainty remains, however, especially in the quantification of other benefits such as visibility or effects on the ecosystem. The process of carrying out a well-documented cost–benefit analysis can add to the transparency of the decision-making process by highlighting the trade-offs inherent in policy-making and helping regulatory agencies set priorities *(21)*. Cost–benefit analysis should be seen, however, as just one of many tools to be used in the process of policy-making, which should be combined with broader social and economic considerations.

Implementation

The process of defining and implementing air quality standards should ensure the establishment of compliance requirements and enforcement regulations as well as mitigation and risk communication strategies, as part of the air quality management framework. In this process the following questions should be addressed.

- How should pollution levels be monitored?
- What criteria should be established to determine compliance with the standards?
- What kinds of mechanism are in place to enforce compliance?
- What control measures should be used to meet the standards?
- How should the public be informed about air pollution management?

Air quality monitoring

A key factor that separates guidelines from standards is the specification of measurement techniques, data handling and analysis. These techniques are specified in air quality standards so that air quality managers can provide relevant data, through the proper characterization of the air pollution situation, to determine if a city or region is in compliance with the standard. The consistent application of monitoring techniques across a country also allows for a more rigorous and fair comparison of pollutant levels in different cities, thereby allowing governments to identify those cities or areas that have the most severe air quality problems.

The monitoring method (automatic, semi-automatic or manual) adopted for each pollutant should be a standard or reference method, or be validated against such methods. The full description of the measurement method should also include information on quality assurance and quality control procedures (internal and external) and on methods of data management, including data treatment, statistical handling of the data and data validation procedures. Quality assurance/quality control procedures are an essential part of the measurement system for reducing and minimizing errors in both the instruments and management of the networks. These procedures should ensure that air quality measurements are consistent and harmonized in the area where the standard is being implemented *(17)*.

Monitoring networks should be designed to inform decision-makers and the public on the population exposures to pollutants. To do so, representative locations are often selected where "typical" air quality is experienced for certain zones (such as city centres and residential or industrial zones). Monitoring networks should also include a site located at a relatively "clean" area in the city of interest. Air pollution levels at this site could be considered as background levels for the monitored pollutant, and may thus serve as a "control". To select representative locations, a screening study could be used to determine the geographical distribution of pollutants, using measurement or modelling techniques. Air quality

monitoring can also be used to determine hot spots or to verify compliance near a known source. The number and distribution of sampling sites required in any network depend on the area to be covered, the spatial variability of the concentrations being measured, and the final use of the data *(22)*.

Air quality monitoring has many other benefits beyond determining compliance with standards. Information from monitoring networks can also be used as an input to exposure and health impact assessments, developing and validating modelling tools, quantifying trends to identify progress or problems, designing policies and setting priorities, and informing people about the quality of the air they breathe *(22)*.

Compliance criteria

When the standards set are to be legally binding, criteria must be identified to determine compliance. This is quantified through the number of acceptable exceedances over a certain period of time. For instance, the annual PM_{10} standard in the United States is not to be exceeded based on the three-year average of the weighted annual mean PM_{10} concentration at each monitor within an area *(4)*. For EU Member States, maximum eight-hour ozone levels may not exceed the target values on more than 25 days per calendar year, averaged over three years *(3)*. In South Africa, the 24-hour nitrogen dioxide standard may not be exceeded more than three times in one year *(9)*.

Compliance criteria are defined in each country in order to compare the most representative data with the standards, and to minimize the designation of non-compliance owing to uncontrollable circumstances such as extreme weather. Such compliance criteria can be determined by evaluating historical data in the region as well as variability in weather and pollution patterns.

Enforcement mechanisms

Responsibilities for overseeing different aspects of compliance can be distributed among local, regional and national governments as well as international organizations, depending on the nature of the air pollution problem and the level at which it is necessary to take action. Compliance with standards may be enforced with regulatory and non-regulatory management approaches. Among these are administrative penalties, obligations to develop mitigation plans, requirements for specific control measures, fines, economic incentives, and voluntary self-mitigation schemes. In the United States, for instance, states are required to develop state implementation plans, in which they identify the control measures that will be implemented to comply with the national ambient air quality standards. Such plans are reviewed and approved by the Environmental Protection Agency, at which point they become federally enforceable.

Specifying legally enforceable compliance mechanisms is of utmost importance in ensuring conformity with air quality standards. Some countries,

however, have adopted standards without incorporating enforcement measures, thereby reducing their effectiveness. If enforcement measures are not included in the regulatory framework, standards become mere guidelines and simply a way of evaluating the magnitude of the air pollution problem. Under such circumstances, information from monitoring networks will be useful only for informing the public, and it will be difficult to compel regions that exceed standards to implement controls.

Air pollution control

In order to reach air quality goals, which may be to stay below air quality standards or to minimize ambient levels of certain pollutants, it is necessary to design effective air pollution control measures. A diverse array of air pollution control measures exists, depending on the specific sources of pollution. In the transportation and industrial sectors, for instance, typical emission controls range from requiring cleaner fuels, to using scrubbers or catalysts to reduce emissions before their release, to changes in engine design, production processes or modes of transportation. Other methods involve measures to change behaviour, such as reducing the demand for electricity or motorized transport.

When defining mitigation strategies to meet air quality standards, important factors to consider include the geographical area that is not meeting the standard and the geographical area for which emission controls should be applied. In determining the geographical scale for abatement strategies, background levels of pollutants and the extent to which pollution is transported from neighbouring areas should be considered. A link between emission controls and ambient air quality is required and may need to be demonstrated. In this sense, good quality emission inventories and dispersion models are fundamental tools for sound air quality management and can be used to evaluate the impacts and effectiveness of certain mitigation measures. Furthermore, cost–benefit analyses can be applied to determine the efficiency of control measures.

Two different frameworks exist in the design of air pollution control policy: command-and-control and market mechanisms. The command-and-control approach refers to the setting of standards to control specific sources. This can be done by specifying emission limits for different emission sources and allowing industries to determine the technology used to meet such standards, or by specifying the technology to be used in reducing emissions. Economists argue, however, that such standards are not efficient, and instead support the use of market mechanisms to reduce air pollution emissions *(23)*. Such approaches include emission capping and trading programmes, which allow industries to emit a limited amount of total pollutants and to trade them between sources, and pollution taxes, which force emitters to meet the costs of the impacts of their emissions *(23)*. Each country should evaluate the array of control options available to it, giving special consideration to their monitoring and enforcement capabilities.

In addition to a comprehensive emissions control programme designed to reduce average pollution levels and meet air quality standards, short-term actions or contingency plans may be applied when pollution episodes occur. Contingency plans should be designed to protect sensitive populations from pollution episodes by including actions to reduce exposures (e.g. avoiding outdoor activities) or rapidly curb emissions (e.g. by reducing vehicular or industrial activity). These measures are not to be confused with long-term goals to reduce overall emissions, improve air quality and reduce population exposures and their associated potential health effects by compliance with air quality standards.

Risk communication

Finally, the proper communication of risks and regulations is a necessary component of air quality management and standards implementation. Communication to all potential stakeholders (including decision-makers, industrial groups, the media and the general public) on issues such as emission sources, ambient pollution levels, population exposures, potential health effects, compliance with standards and control options is fundamental in achieving sound environmental management. Public opinion can be an important factor in influencing decisions, as the political capability of decision-makers is directly proportional to the interests and concerns of their constituents. Research has found that resources will often be directed to where the public perceives risks to be large, whether or not they represent the most serious hazards to society *(14)*. When people understand the importance of air quality, they can demand action and be more receptive in complying with control measures. It is therefore in the interest of environmental and health authorities to ensure that the public is informed and educated about air pollution levels, sources, health impacts and possible solutions.

Maintaining an active communication strategy throughout the whole air quality management process may also help prevent crises, conciliate interests, provide advance notice for the implementation of control measures and inform stakeholders on compliance status. For these reasons, the development of communications tools that are understandable and accessible to the public is an important part of air quality management.

People should be informed as to how their city/region/country is doing in terms of air quality, and what that means for their health. The use of air quality indices, such as the Metropolitan Air Quality Index used in Mexico City *(24)* or the Air Quality Index in the United States *(25)*, are useful communication tools in translating technical air pollution information into information that the public can understand and use. Providing this information can help prevent acute exposures and symptoms by warning the public about high pollution levels and suggesting simple actions that can be taken to prevent exposure.

Frequent or even occasional application of contingency measures can maintain population awareness and highlight the seriousness of air pollution problems by

generating intensive media attention. Owing to the severe measures commonly used in contingency plans that affect the behavioural patterns of the population, when episodes occur these plans can be very effective in underlining the importance of action to improve air quality.

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9. Indoor air quality[1]

Kalpana Balakrishnan, Nigel Bruce

Summary

The indoor environment represents an important microenvironment in which people spend a large part of their time each day. There are great differences in sources, pollutants, health risks and opportunities for indoor air quality management between developed and developing countries. Noting the substantial nature of these differences and consequences for air quality guidelines, this chapter is particularly devoted to indoor air quality associated with domestic solid fuel use in developing countries. About half of the world's population, largely in developing countries, relies on traditional fuels such as biomass (wood, agricultural residues and animal dung), charcoal and coal as the primary source of domestic energy. Use of solid fuels in open or poorly ventilated stoves for cooking and heating exposes an estimated three billion people to high concentrations of PM and gases that are some 10–20 times higher than levels commonly found in international health guidelines (including the WHO air quality guidelines). Recent studies estimate that exposure to indoor air pollutants associated with household solid fuel use may be responsible for nearly 1.6 million excess deaths and about 3% of the global burden of disease.

Although current scientific knowledge on this issue and the highly decentralized and heterogeneous nature of exposure may not permit a numerical guideline value to be recommended for such indoor exposures (similar to those for pollutants in outdoor air), they do permit several risk management strategies to be identified. This chapter describes the extent and magnitude of such indoor exposures, the consequent health risks and possible options for interventions. Recommendations are made for a phased approach to the development of air quality guidelines for indoor air quality management in developing countries, recognizing the urgent need for action, the limitations of evidence and the paucity of exposure data but also the opportunities offered by a set of interim guidelines.

[1] The authors gratefully acknowledge the comments and technical advice provided by Professor Kirk Smith, University of California School of Public Health, Berkeley, in the preparation of this chapter.

Background

Indoor air pollution issues

The indoor environment represents an important microenvironment in which people spend a large part of their time each day. As a result, indoor air pollution, originating from both outdoor and indoor sources, is likely to contribute more to population exposure than the outdoor environment. The extent and magnitude of consequent health risks, however, remain poorly understood. The large number of indoor air pollutants, including chemical and biological contaminants, and the influence of a variety of factors such as the nature and location of sources, air exchange between indoor and outdoor environments and individual behaviour make accurate estimations of health effects very difficult.

The major sources of indoor air pollution worldwide include combustion of solid fuels indoors, tobacco smoking, outdoor air pollutants, emissions from construction materials and furnishings, and improper maintenance of ventilation and air conditioning systems (Table 1) *(1)*. There are, however, marked variations in the importance of these different sources in different areas of the world, closely related to level of socioeconomic development.

Although relatively clean sources of household energy predominate in developed countries, improvements in energy efficiency have led to homes being relatively airtight, reducing ventilation and raising indoor pollutant levels. In

Table 1. Major health-damaging pollutants generated from indoor sources

Pollutant	Major indoor sources
Fine particles	Fuel/tobacco combustion, cleaning operations, cooking
Carbon monoxide	Fuel/tobacco combustion
Polycyclic aromatic hydrocarbons	Fuel/tobacco combustion, cooking
Nitrogen oxides	Fuel combustion
Sulfur oxides	Coal combustion
Arsenic and fluorine	Coal combustion
Volatile and semi-volatile organic compounds	Fuel/tobacco combustion, consumer products, furnishings, construction materials, cooking
Aldehydes	Furnishings, construction materials, cooking
Pesticides	Consumer products, dust from outside
Asbestos	Remodelling/demolition of construction materials
Lead	Remodelling/demolition of painted surfaces
Biological pollutants	Damp materials/furnishings, components of climate control systems, occupants, outdoor air, pets
Radon	Soil under buildings, construction materials
Free radicals and other short-lived, highly reactive compounds	Indoor chemistry

Source: Zhang & Smith *(1)*.

such circumstances even minor sources of pollution, such as gas cookers, new furnishings, damp conditions, household products or naturally occurring radon gas, can lead to significant exposures and recognized health effects *(2)*. Together with environmental tobacco smoke, gases such as nitrogen dioxide, radon and bio-aerosols dominate air quality concerns in developed countries. There are also growing concerns about volatile or semi-volatile chemicals emitted from materials and products to indoor air.

In developing countries, the most significant issue for indoor air quality is exposure to pollutants released during combustion of solid fuels, including biomass (wood, dung and crop residues) or coal (mainly in China), used for cooking and heating. The majority of households using such fuels are located in poor rural communities and use inefficient devices such as earthen or metal stoves in kitchens that are often poorly ventilated, resulting in very high exposures. Consequently, pollutant profiles and the resulting exposure profile and health risks are also very different between developed and developing countries, although some (including environmental tobacco smoke) are likely to be of concern in both settings. In developing countries, high (often very high) levels of particulates and other products from the incomplete combustion of solid fuels are the major concerns.

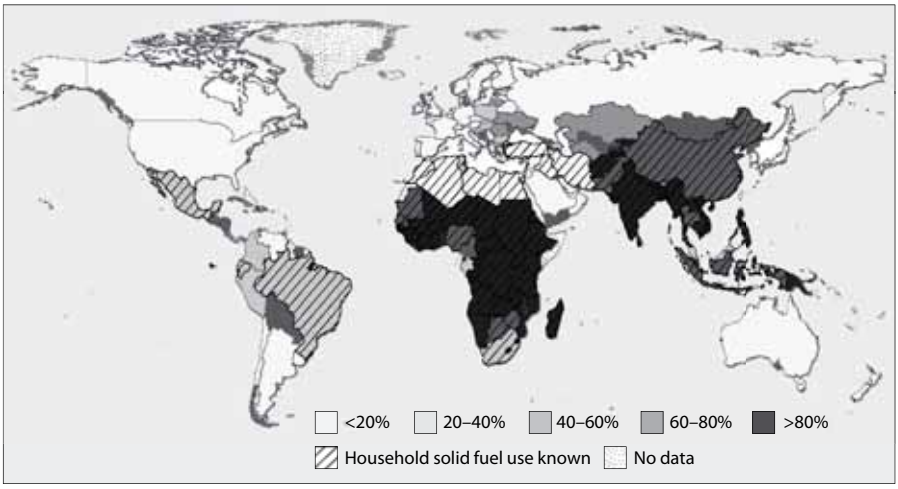
Indoor air pollutants have not been as extensively monitored as outdoor air pollutants, even in developed countries, and the evidence base for contributions to health effects needs to be strengthened. Most developed countries, however, have the infrastructure required to support an indoor air quality management strategy, and in some countries such strategies are already being implemented *(3)*. In contrast, the problem of indoor air pollution from solid fuel use in developing countries is set against a backdrop of vulnerable populations, competing risks from multiple other environmental health risks, inadequate technical resources for generation of additional scientific evidence, limited feasibility of technological interventions, relative inexperience in implementing air quality management programmes and limited local capacity for environmental management. These factors, together with the sheer size of the population at risk, demand an approach to the formulation and application of air quality guidelines that differs markedly from that hitherto followed in developed countries.

In view of the substantial global burden of disease from solid fuel use, together with these important differences in sources, pollutants, health risks and opportunities for air quality management, this chapter is specially devoted to indoor air pollution issues associated with domestic solid fuel use in developing countries. A number of other sources provide excellent accounts of indoor air pollution issues in developed countries *(4–6)*.

Indoor air pollution associated with solid fuel use in developing countries

About half of the world's population, largely in developing countries, relies on traditional solid fuels such as biomass (wood, agricultural residues and animal dung), charcoal and coal as the primary source of domestic energy *(7,8)*. Fig. 1 shows the relative prevalence of solid fuel use across the world. Exposure to indoor air pollutants released during combustion of these solid fuels is the most significant factor affecting indoor air quality in homes in developing countries.

Fig. 1. Household solid fuel use across the world, 2000



Source: Smith et al. *(9)*.

Household fuel demands have been shown to account for more than half of the total energy demand in most countries with annual per capita incomes under US$ 1000, while accounting for less than 2% in industrialized countries *(10)*. As per capita incomes increase, households switch to cleaner, more efficient energy systems for their domestic energy needs (i.e. move up the "energy ladder"), [2] owing largely to increases in affordability and demand for greater convenience and energy efficiency. With technological progress, the income levels at which people make the transition to cleaner fuels has fallen *(10)*. Despite the availability[3] of

[2] The energy ladder *(12)* is made up of several rungs, with traditional fuels such as wood, dung and crop residues occupying the lowest rung. Charcoal, coal, kerosene, gas and electricity, in that order, represent the next steps up the ladder. As one moves up the energy ladder, energy efficiency and costs increase while pollutant emissions typically decline. While several factors influence the choice of household energy (and moving up the energy ladder may not be determined simply by household income *(13)*) the use of traditional fuels and poverty are closely interlinked.

[3] This is really "potential" availability, as there is a vicious circle of poverty resulting in low demand, which in turn results in poorly developed products and services (e.g. financing) and inadequate supply/marketing, making it even harder for poor households to access these fuels and keeping demand low.

cleaner fuels, however, many rural areas continue to use solid fuels as a result of opportunities for free (in monetary terms) collection of biomass, sociocultural preferences or as a way of protecting the household against an unreliable supply of such cleaner fuels *(11)*. Household fuel supply, distribution and consumption are thus closely related to the overall status of energy, environment and development in countries.

The magnitude of environmental and health damage as a result of the widespread use of traditional solid fuels, including biomass, has only recently begun to receive the attention of researchers and policy-makers worldwide. The use of open fires for cooking and heating exposes an estimated three billion people in the world to enhanced concentrations of PM, health-damaging gases and, in some settings, toxic substances such as arsenic and fluorine (from the use of coal) up to 10–20 times higher than set out in commonly used health guidelines (for example, the WHO air quality guidelines or the national ambient air quality standards set by the US Environmental Protection Agency (USEPA). Also, 10–20% of households in developing countries use kerosene for cooking *(10)*. When supplies of kerosene are limited, such households have been reported to switch back to solid fuels or to use kerosene together with solid fuels *(14)*. Although indoor particulate emissions from kerosene are lower than those from solid fuels, other pollutants such as nitrogen dioxide, sulfur dioxide and volatile and semi-volatile organic compounds may be of concern in these homes *(15–18)*.

Several studies in developing countries *(9,19,20)* have provided persuasive evidence for associations between the use of solid fuel (mainly biomass) and increased incidence of chronic bronchitis in women, acute respiratory infections in children and, where coal is used, lung cancer. In addition, evidence is now emerging of links with a number of other conditions, including perinatal mortality, low birth weight, asthma, tuberculosis, cataracts and cancer of the upper airways. Recent interest in the effects of air pollution on cardiovascular disease (CVD) raises the question as to whether pollution from solid fuel combustion also increases the risk of CVD in developing countries. Empirical work from developing countries on indoor air pollution and CVD is awaited. Health effects may also be associated with kerosene or mixed kerosene/solid fuel use, but limited information is available to specifically characterize risks attributable to kerosene.

The recently concluded comparative risk assessment exercise conducted by WHO estimates that exposure to indoor smoke from solid fuels may be responsible for about 1.6 million premature deaths annually in developing countries and nearly 3% of the global burden of disease *(9)*.

Although current scientific knowledge on this issue and the highly decentralized and heterogeneous nature of exposure may not permit a numerical guideline value to be recommended for such indoor exposures (similar to those for pollutants in outdoor air), they do permit several risk management strategies to be identified. The following sections describe the extent and magnitude of such

indoor exposures, the consequent health risks and possible options for interventions. Recommendations are made for a phased approach to the development of air quality guidelines for indoor air quality management in developing countries, recognizing the urgent need for action, the limitations of evidence and the paucity of exposure data but also the opportunities offered by a set of interim guidelines.

Characteristics of solid fuel smoke

Air pollutant emissions from solid fuels are the result of incomplete combustion, conditions for efficient combustion being difficult to achieve in stoves typically found in homes in poor developing countries. The amount and characteristics of pollutants produced during burning depend on several factors, including fuel composition (including water content), combustion conditions (temperature, air flow and humidity), mode of burning, and even the shape of the fireplace *(15)*. A very large number of different chemical substances are emitted during the burning of biomass fuels in the form of gases and aerosols (suspended liquids and solids). These pollutants include carbon monoxide, nitrogen dioxide, particles (largely in the range below 10 μm in aerodynamic diameter) and other organic matter predominantly composed of polycyclic aromatic hydrocarbons (PAHs) such as benzo[*a*]pyrene and other volatile organic compounds such as benzene and formaldehyde *(15,21)*. Combustion of coal in addition to the above pollutants may release oxides of sulfur and toxic elements including arsenic and fluorine *(22)*. Smoke from wood-burning stoves has been shown to contain 17 substances designated as priority pollutants by USEPA because of their toxicity in animal studies, up to 14 carcinogenic compounds, 6 cilia-toxic and mucus-coagulating agents and 4 co-carcinogenic or cancer-promoting agents *(23,24)* (Table 2).

Indoor air pollutant levels in households using solid fuel: concentrations and exposures

The majority of households in developing countries burn solid fuels in poorly functioning earth or metal stoves or use open pits. Incomplete combustion in poorly ventilated kitchens[4] thus results in very high levels of indoor air pollution. Well over a hundred studies over the last two decades have assessed levels of indoor air pollutants in households using solid fuels. The methods employed range

[4] In many rural households in developing countries, it is common to find kitchens with limited ventilation being used for cooking and other household activities. Even when the kitchen is separated from the living areas, in most cases it is very easy for the smoke to diffuse across. Use of biomass for space heating creates additional potential for exposure to smoke in living areas. It may be noted, however, that air exchange rates encountered in many village homes in developing countries range from 10 to 15 per hour, much higher than the 1–2 per hour for homes in developed countries *(33)*. Poor ventilation thus largely results from the presence of a very strong emission source (the stove) with limited possibilities for extracting pollutants at source (i.e. stoves are usually without flues and rooms are often without chimneys or have only small openings).

Table 2. Toxic pollutants from biomass combustion and potential for toxicity

Pollutant	Known toxicological characteristics
Particulates (PM_{10}, $PM_{2.5}$)	Bronchial irritation, inflammation, increased reactivity, reduced mucociliary clearance, reduced macrophage response
Carbon monoxide	Reduced oxygen delivery to tissues owing to formation of carboxyhaemoglobin
Nitrogen dioxide (relatively small amounts from low-temperature combustion)	Bronchial reactivity, increased susceptibility to bacterial and viral lung infections
Sulfur dioxide (relatively small amounts from most biofuels)	Bronchial reactivity (other toxic end-points common to particulate fractions)
Organic air pollutants	
formaldehyde	Carcinogenicity
1,3-butadiene	Co-carcinogenicity
benzene	Mucus coagulation, cilia toxicity
acetaldehyde	Increased allergic sensitization
phenols	Increased airway reactivity
pyrene	
benzo[*a*]pyrene	
dibenzopyrenes	
dibenzocarbazoles	
cresols	

Sources: Bruce, Perez-Padilla & Albalak *(19)*; Cooper *(23)*; Smith *(15)*; Smith & Liu *(24)*.

from collecting questionnaire-based information to quantitative measurements of household exposures.[5] A global database is now available that documents results of these measurements from about 110 studies in China and about 70 studies in developing countries in Asia, Latin America and Africa *(26)*. Although the great majority of studies have performed single-pollutant measurements on a cross-sectional sample of households, some recent studies have made important contributions to examining temporal, spatial or multi-pollutant patterns in addition to day-to-day or seasonal variability in concentrations and exposures *(14,26–31)*. A few have also developed models to examine the differential contributions of household-level determinants and validate the use of simpler household-level indicators (that are relatively easy to collect) as a proxy for household exposures *(14,32)*.

[5] Exposures refer to the concentration of pollutants in the breathing zone during specific periods of time. Exposures reflect what is likely to be the internal body dose, the key determinant of health effects. Individual exposures would therefore be determined not only by the concentrations of pollutants but also by how long an individual spends breathing the polluted air. Those who cook or who stay close to the stove while cooking, and young children who spend a considerable amount of time in the kitchen, are thus likely to receive the highest exposures. Those who do not cook, despite living in the same households with high concentrations, have lower exposures. Some studies have measured only ambient air concentrations (e.g. at breathing height near the stove) with or without time–activity information to assess exposures. Others have involved fitting people with monitors, which allow for time spent close to sources (but also pick up pollution from sources other than the person's own stove).

Findings for particulates from selected studies carried out since 1990 in developing countries are shown in Table 3. Fewer studies have included measurement of nitrogen dioxide and sulfur dioxide, both of which are the subject of chapters in this book. For nitrogen dioxide, values in homes in developing countries have been reported in the following ranges ($\mu g/m^3$) for various fuels measured during cooking or for periods of between 8 and 24 hours: wood from <100 to several hundred, coal from several hundred to nearly 1000, kerosene from <30 to nearly

Table 3. Comparison of particulate levels as determined in some recent studies in developing countries

Location	Averaging time/ size fraction	Type of fuel	Mean levels/range ($\mu g/m^3$)
1. Nepal *(34)*	Cooking period/$PM_{2.5}$	Wood/crop residues	8200 (traditional stove) 3000 (improved stove)
2. Garhwal, India *(26)*	Cooking period/TSP	Wood/shrubs	4500 (GM)
	24-h exposure/TSP		700–1690 (winter) 250–1130 (summer)
3. Pune, India *(35)*	12–24 h/PM_{10}	Wood	2000 (area) 1100 (personal)
4. Mozambique *(36)*	Cooking period/PM_{10}	Wood	1200
5. Rural Bolivia *(37)*	6 h/PM_{10}	Dung	1830 (GM, indoor kitchens) 280 (GM, outdoor kitchens)
6. Kenya *(28,29)*	Daily average exposure/PM_{10}	Mixed	1000–4800
7. Tamil Nadu, India *(27)*	Cooking period/ respirable fraction (d_{50} = 4 µm)	Wood/ agricultural waste	1307–1535 (GM, personal)
	Daily average exposure/respirable fraction (d_{50} = 4 µm)	Wood/ agricultural waste	172–226
8. Guatemala *(38)*	24 h/$PM_{3.5}$	Wood	1560 (GM, traditional stove) 250 (GM, improved stove) 850 (GM, LPG/open fire combination)
9. Andhra Pradesh, India *(14)*	24 h/respirable fraction (d_{50}=4 µm)	Wood/dung/ agricultural waste	297–666 (kitchen area) 215–357 (living area)
	Daily average exposure/respirable fraction (d_{50}=4 µm)	Wood/dung/ agricultural waste	431–467
10 Bangladesh *(39)*	24 h/PM_{10}	Wood/dung/ agricultural waste	196–264 (personal) 60–1165 (area)

Note. GM = geometric mean; TSP = total suspended particulates; RSP = respirable suspended particulates.

200, and LPG (liquefied petroleum gas) from <10 to nearly 200 *(26)*. For sulfur dioxide, values reported for wood range from <30 to nearly 200, for coal (geometric mean) <100 to nearly 1000, for kerosene <50 to over 100, and for LPG <25 to several hundred. Mixed fuel use was recorded in many of these studies, resulting in further variations in levels and patterns of exposure. Further, in many poor homes, solid fuels are used for heating as well as cooking. Heating requires the stove to be used for much longer periods and increases the potential for exposure several-fold. The spatial, temporal and demographic patterns in exposures can be quite different when solid fuels are used for cooking only as against both cooking and heating *(26,31)*.

Lack of uniformity in methods (varying study designs and measurement protocols), small sample sizes, differences in the profiles of exposure determinants and local research capacity limitations have made it somewhat difficult to draw comparisons across studies. The collective evidence from these studies shows, however, that people in rural settings where solid fuel is used are exposed to extremely high levels of particulates, gases and other noxious pollutants, often an order of magnitude higher than guideline levels.

Guideline levels for nitrogen dioxide and sulfur dioxide are also exceeded for households using kerosene and LPG in some studies, although contributions from other fuels and pollution sources in the locality may be important. Some emissions from coal combustion, including arsenic and fluorine, also have potential non-inhalational exposure routes (such as deposition on food and contamination of drinking-water sources) that compound health effects *(30)*.

Biomass use is not uncommon among the urban as well as the rural poor. These populations, often living in meagre dwellings at the side of busy roads, face risks from both indoor and outdoor emissions *(40)*. Children and adults may be exposed in other settings outside the home. For example, many community school programmes in India providing free midday meals to children use biomass fuels in kitchens that are often adjacent to classrooms. Exposures from solid fuels are therefore not limited to rural household settings. Very limited information is currently available, however, with which to assess the scale and level of such exposure.

Health effects associated with exposure to solid fuel smoke

Evidence for health effects associated with exposure to smoke from the combustion of biomass fuels was provided initially by studies on outdoor air pollution as well as by those dealing with exposure to environmental tobacco smoke. Criteria documents for outdoor air pollutants published by USEPA *(41)*, for example, detail the effects of many components also found in wood smoke, including PM, carbon monoxide, oxides of sulfur and nitrogen and PAHs.

Considerable scientific understanding now exists about the aerodynamic properties of particles that govern their penetration and deposition in the respiratory

tract. The health effects of particles deposited in the airways depend on the defence mechanisms of the lung such as aerodynamic filtration, mucociliary clearance and in situ detoxification. Since most PM in biomass fuel smoke is less than 3 μm in diameter, it is likely to reach the deepest portions of the respiratory tract and alter defence mechanisms. Several biomass fuel combustion products may also impair mucociliary activity and reduce the clearance capacity of the lung, leading to increased residence time of inhaled particles, including microorganisms. In situ detoxification, the main defence mechanism in the deepest non-ciliated portions of the lung, may also be compromised by exposure to components of biomass fuel smoke *(42)*.

Among the gaseous pollutants, carbon monoxide is known to bind to haemoglobin (thereby reducing oxygen delivery to key organs) and may have important implications for pregnant women, the developing fetus being particularly vulnerable. Studies measuring carbon monoxide exposure have shown levels generally up to (and occasionally in excess of) those in existing WHO guidelines, but the effects of the long-term exposure of women (especially when pregnant) and children to these concentrations are poorly understood. Although emissions of other gases such as sulfur dioxide and nitrogen dioxide are of lesser concern in biomass combustion (very high levels of sulfur dioxide may be reached with other solid fuels such as coal), they are known to increase bronchial reactivity. PAHs such as benzo[*a*]pyrene are known carcinogens.

Some of the earliest human evidence linking indoor air pollution from solid fuel combustion with respiratory health came from studies carried out in Nepal and India in the mid-1980s *(44)*. Since then, there have been a few new studies, especially on women who cook with these fuels, and on young children. Associations between exposure to indoor air pollution and increased incidence of chronic bronchitis in women, acute lower respiratory infections (ALRI) in children and lung cancer (in coal users) have been documented *(9,19)*. Odds ratios[6] in the range of 2–5 have been reported for the incidence of acute respiratory infections in children exposed to biomass smoke. The incidence of COPD in non-smoking women using biomass for cooking has also been shown to depend on the number of years of cooking with biomass and often to be comparable to that of men (who usually have high smoking rates) *(44)*. Odds ratios of 1.17–1.86 have been reported for lung cancer among coal users *(9)*.

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[6] Odds ratios represent the ratio of the probability of occurrence to non-occurrence of an event. Two types of odds ratio are commonly used in epidemiological studies. The disease odds ratio (or risk odds ratio) is the ratio of (the odds of disease for those with some exposure) to (the odds of disease for those without the exposure). The exposure odds ratio is the ratio of (the odds of exposure for those with disease) to (the odds of exposure for those without disease). The papers cited above have used a disease odds ratio. For example, an odds ratio of 2 for ARI in children for households burning biomass would imply that the odds of these children suffering from ARI is twice that of a reference group of children in households using a "clean" fuel (gas).

Evidence has also been reported for a link with other health outcomes, including asthma, tuberculosis, cataracts and adverse perinatal outcomes. Associations between increased fine particulate levels and asthma have been reported in the literature on urban air pollution and ETS *(45,46)*. With levels of fine particulates much higher in homes using solid fuel, such associations with asthma are likely for indoor air pollution as well. Studies in China *(47)* and Kenya *(48)* have reported positive associations of asthma in schoolchildren with various measures of indoor air pollution. Studies in India *(49,50)* and Mexico *(51,52)* have reported increase risks of tuberculosis amongst biomass users. Studies on increased risks of cataracts amongst biomass users have been reported in India *(49,53)*. Excess risks of adverse perinatal outcomes, including stillbirth and low birth weight have also been reported for biomass users *(54,55)*. Like asthma, it seems plausible that indoor air pollution is associated with adverse pregnancy outcomes, as they too have been associated with outdoor air pollution and smoking *(56,57)*.

Most studies on the health effects of biomass combustion have been observational and have relied on proxy measures of exposure (such as reported hours spent near the stove, years of cooking experience, or child being carried by the mother while cooking). While the use of solid fuels results in substantially higher concentrations in these households compared to those using gas or other modern fuels, within- and between-household differences found in homes using any given fuel type can be substantial. Differences in individual exposures can be masked significantly by such binary exposure classification schemes and result in ambiguity in health impact assessments. Although not all studies have addressed confounding, the majority have and adjustment has not markedly affected the findings. Confounding may, however, be difficult to fully account for in situations typically found in poor rural communities, where the other major risk factors for some health outcomes such as ALRI are closely associated with poverty and fuel use and housing conditions that affect ventilation and exposure *(58)*. Despite these uncertainties, the consistency of evidence from studies exclusively carried out in developing countries, together with supportive evidence provided

Table 4. Health effects of exposure to smoke from solid fuel use: plausible ranges of relative risk in households using solid fuel

Health outcome	Population affected	Relative risk		Strength of evidence
		Low	High	
ALRI	<5 years	2.0	3.0	Strong
Asthma	Females ≥15 years	1.4	2.5	Intermediate/moderate
Blindness (cataracts)	Females ≥15 years	1.3	1.6	Intermediate/moderate
COPD	Females ≥15 years	2.0	4.0	Strong
Lung cancer (coal use only)	Females ≥15 years	3.0	5.0	Strong
Tuberculosis	Females ≥15 years	1.5	3.0	Intermediate/moderate

Source: Smith et al. *(21)*.

Table 5. Summary of relative risk estimates for health outcomes used in 2002 estimates of burden of disease

Health outcome	Age and sex group	No. of studies	Relative risk	95% CI
ALRI	Children <5 years	8	2.3	1.9–2.7
COPD	Women >30 years	8	3.2	2.3–4.8
	Men >30 years	2	1.8	1.0–3.2
Lung cancer (coal use only)	Women >30 years	9	1.9	1.1–3.5
	Men >30 years	3	1.5	1.0–2.5

Source: Smith et al. *(9)*.

by studies on outdoor air pollution and ETS, indicates that there is likely to be a strong association between indoor smoke exposure and ALRI in children, COPD among women and lung cancer (where coal is used). The evidence for other health outcomes needs to be further evaluated through studies with more rigorous exposure assessment and control of confounding. Tables 4 and 5 show relative risk estimates for health outcomes that are associated with exposure to smoke from solid fuel *(9)*.

For computing disease burdens associated with solid fuel use, estimates of relative risk obtained from epidemiological studies have been combined in meta-analyses for the three disease end-points for which there is strong evidence of an association with use of solid fuels, namely ALRI in children aged <5 years, COPD and lung cancer (coal use only) (Table 5). Using these risk ratios, the recently completed WHO global comparative quantification of health risks *(9)* estimates that more than 1.6 million deaths and over 38.5 million disability-adjusted life years (DALYs) were attributable to indoor smoke from solid fuels in 2000. Cooking with solid fuels is thus responsible for a significant proportion, about 3%, of the global burden of disease. These risks are comparable to risks from tobacco use and are only exceeded by malnutrition (16%), unsafe water and sanitation (9%) and unsafe sex (4%).

The inverse association between burden of disease from indoor air pollution and level of economic development (Table 6), borne out at subregional levels, emphasizes the need for addressing indoor air pollution in the mainstream of poverty alleviation initiatives. ALRI is the leading cause of disease burden in children under five years. It contributes the most (up to 80%) to deaths and DALYs attributable to indoor air pollution in most settings where solid fuel is used, thereby indicating the need for special child health initiatives to address this issue. Women, who are the main caregivers in the family, bear a significant disease burden that can have implications beyond their own health (most importantly their children's health). There are thus complex links among the health risks from indoor air pollution in household settings, and an overall understanding of these links is crucial to the design of mitigation strategies.

Table 6. Burden of disease associated with solid fuel use across world regions

Subregion	Deaths (thousands)				DALYs (thousands)			
	ALRI	COPD	Lung cancer	All causes	ALRI	COPD	Lung cancer	All causes
AFR-D	153	20	NA [a]	173	5 221	173	NA	5 394
AFR-E	198	21	NA	219	6 746	178	NA	6 924
AMR-A	0	0	NA	1	1	6	NA	6
AMR-B	6	9	NA	16	291	153	NA	444
AMR-D	9	2	NA	10	314	16	NA	330
EMR-B	2	0	NA	2	59	5	NA	64
EMR-D	94	22	NA	116	3 306	203	NA	3 508
EUR-A	0	0	NA	0	0	0	NA	0
EUR-B	12	5	NA	17	417	60	NA	477
EUR-C	1	4	NA	4	22	44	NA	67
SEAR-B	19	17	NA	37	761	229	NA	990
SEAR-D	355	167	1	522	12 506	1 724	8	14 237
WPR-A	0	0	NA	0	0	0	NA	0
WPR-B	62	426	15	503	2 275	3 662	160	6 097
World	910	693	16	1 619	31 919	6 453	168	38 539

[a] Not applicable.
Source: Smith et al. *(9)*.

Comparability of health impacts from indoor and outdoor air pollution

One key issue in the assessment of health risks associated with indoor air pollution from solid fuel use in developing countries is whether the characteristics of the pollution (especially PM, being the single most studied and most important health-damaging pollutant) differ in any substantial way from that in outdoor air. This reflects the different sources of pollution and settings for health risk assessment: household use of mainly unprocessed biomass in developing countries compared to the use of mainly fossil fuels in urban settings in the developed world, where the great majority of air pollution epidemiology has been conducted to date.

As and when there is a sufficiently robust and comprehensive evidence base of quantitative health risk assessments linked with indoor air pollution from developing countries, this issue will be of less relevance. However, such an evidence base is likely to be decades away, for two main reasons. First, most epidemiological studies of indoor air pollution and health risks in developing countries to date have used proxies for exposure, making it rather difficult to quantify the exposure–outcome relationship based on current evidence. Second, conducting new studies for the range of health outcomes currently of concern presents considerable challenges in terms of all main aspects of study design (ensuring effective

exposure reduction, avoiding confounding, measuring exposure and health outcomes), funding and local research capacity.

Previous reports have taken the view that evidence is currently insufficient to justify applying ambient (outdoor) air quality guidelines to indoor air pollution from solid fuels in developing countries *(2)*. Although, as noted above, the level of evidence on exposure–outcome relationships for such pollution has not changed substantially in the last few years, the weight and consistency of evidence using indirect measures has been growing steadily. Furthermore, based on a review of the toxicology of PM and studies of biomass (mainly wood) smoke health effects in developed countries, it is concluded in Chapter 10 that there is "little evidence to suggest reduced or altered toxicity from these [biomass smoke] particles relative to the more commonly studied urban air PM", despite there being acknowledged differences in composition and physical attributes. It has also been pointed out that environmental tobacco smoke, itself a form of fresh biomass pollution quite similar in many ways to smoke from wood and other routinely used household biomass fuels, entails well-documented risks for a similar range of health outcomes, typically at somewhat lower exposure levels *(2)*.

Given the recent evidence from systematic reviews and meta-analyses used for the WHO comparative risk assessment exercise *(9)* and that from studies of health risks of ETS (and the fact that exposure occurs both indoors and outdoors for all the pollutants involved) it is reasonable now to propose using the same air quality guidelines for both indoor and outdoor exposures. Crucially, however, there is currently a lack of data on indoor air pollution and exposure in vulnerable populations, and such data are unlikely to become available in the short (or even medium) term. This means that the applicability of exposure–outcome data derived from outdoor air pollution studies to solid fuel use in households in developing countries is not in practice the most critical issue for most of the countries concerned. Rather, the priority is for the development and evaluation of guidelines that can be realistically assessed in communities most at risk, and translated into standards that are relevant to those responsible for developing and implementing policy in order to reduce exposure in these communities. The implications for actual guidelines are discussed further in the concluding sections of this chapter.

Options for interventions

Contributions both from technology (e.g. fuel/stove switches, ventilation design) and from policies and programmes (e.g. awareness raising, technology training, market development, financing mechanisms) are required for the design of effective risk reduction/intervention programmes for indoor air pollution. This section describes several options that have been deployed across the world. It is important to recognize, however, that these specific technologies and approaches do not represent generally applicable solutions, since effectiveness and acceptability

are highly dependent on local circumstances and needs. The description of options should therefore be viewed as a framework from which appropriate packages can be developed for local situations, incorporating lessons learnt from situations elsewhere.

Recent reviews describe the use of a variety of indoor air pollution interventions *(59,60)*. Broadly speaking, they have centred on reducing indoor air pollution in three ways: by producing less smoke (improved stoves, improved biomass fuels, switching to cleaner fuels); by removing smoke from the indoor environment (chimneys, flues, hoods, ventilation); and by reducing exposure to smoke (reducing cooking time, behaviour, kitchen design).

Improved fuels are usually more efficient and produce less smoke. Considerable evidence is available to indicate that gaseous fuels such as LPG and liquid fuels such as kerosene produce considerably lower pollution levels than solid fuels *(11,14,27,38)*. One study also showed significant reductions in indoor air pollution levels in homes following electrification in rural South Africa, despite only a partial switch to electricity for cooking *(61)*. Some biomass-derived fuels, such as briquettes, biogas, producer gas and bio-diesel, have been engineered to burn cleaner. A recent study in sub-Saharan Africa showed that a shift from firewood to charcoal or fossil fuels would produce a greater than 90% reduction in indoor air pollutant levels, with a simultaneous reduction in greenhouse gas emissions, if accompanied by appropriate use of technology and land management *(62)*. Despite much lower emissions, these fuels have not yet seen widespread use. Switching to cleaner fuels is not currently a feasible option for most poor communities in developing countries for many reasons. For example, provision of electricity to rural homes requires extensive infrastructure, and most poor people with access to electricity can afford to use it only for lighting and other low-demand electrical appliances. Cost and availability also limit the use of LPG and kerosene in most developing countries. Without marked improvements in socioeconomic conditions, awareness of benefits and appropriate financing initiatives, general improvement in access to clean fuels seems to offer little potential to bring about substantial reductions in indoor air pollution.

Improved stoves that burn fuel more efficiently and vent emissions[7] to the outside have been an intervention option for more than two decades. Improved stove programmes have been carried out in many countries, most notably India and China. These programmes, although initially designed to conserve wood used as fuel, affect emissions of both health-damaging pollutants and greenhouse gases *(63,64)*. Stove models with flues that result in substantially lower

[7] Improved efficiency is not always accompanied by reduced emissions. An increase in efficiency may be accomplished merely by increasing the heat transfer efficiency, in which case emissions (which are directly related to fuel combustion) are not reduced. Further, expected gains in efficiency (established under laboratory conditions) are seldom realized under field conditions, most improved stoves providing a less than 25% saving in fuel consumption.

indoor concentrations of pollutants have also been documented in many regions – China *(65)*, India *(13,66)*, Nepal *(34,67)*, Latin America *(38,68,69)*, Mexico *(70)* and sub-Saharan Africa *(13,28,29,71)*. Although substantial reductions have been achieved with many of these models, the residual levels are still high compared to health-based air quality guidelines available for outdoor settings. In some instances, while room (area) levels of pollutants were significantly reduced, the reduction in personal exposure was proportionately less. In Kenya, for example, where hoods with flues achieved a 75% reduction in 24-hour mean kitchen $PM_{3.5}$ and carbon monoxide, the mean 24-hour exposure of women to carbon monoxide was reduced by only 35% *(71)*. Similar results were found for exposure of children in a study of improved wood stoves in Guatemala *(30)*. In a recent review of the Chinese improved stove programme, several challenges in implementing as well as assessing the efficacy of the interventions were documented *(65)*. Problems cited include difficulties in extending the programme to large populations, deterioration of efficiency over time owing to poor maintenance, use of improved stoves for cooking without simultaneous replacement of stoves used for heating, and lack of simultaneous emphasis on reducing indoor air pollution and energy efficiency.

Moreover, many factors have been shown to determine the acceptability of improved stoves among communities, including market environments, sociocultural preferences, capital and running costs, and access to clean fuels. Except in arid areas, rural populations are often under little pressure to conserve wood and are not willing to spend any additional resources on alternative fuels or stoves. Indeed, when fuel wood becomes scarce, people have been known to move down the energy ladder and shift to agricultural (crop) wastes and animal dung, which are known to be more polluting *(12)*. In China, the wide availability of a range of improved biomass stoves has reduced emissions and exposures for households using biomass. The improved biomass stove programme was introduced to support local policy to limit biomass use. However, although exposures in biomass-using households were reduced, the reduced access to biomass and the easy availability of coal (often of inferior quality and contaminated with toxic elements such as arsenic and fluorine) meant that many communities switched to using coal. Use of coal stoves without chimneys produces greater pollution than the original biomass stoves *(63)*. Generally, it appears that perceptions of health risks currently play a very limited role in determining the energy choices that people make in their daily lives. Improved stoves may thus remain a feasible indoor air pollution intervention in the short term, but past experience in many countries queries their effectiveness in the long term.

Interventions that reduce exposure either by changing behaviour or by improving ventilation have also been described *(71)*, but the evidence for reductions in exposure and health risks currently available from such studies is quite limited.

Most evidence available for assessing the effectiveness of interventions deals with the impact on indoor air pollution levels and, in some cases, personal exposure. There is, however, no experimentally derived evidence on the effect of reducing indoor air pollution exposure on the incidence of ALRI or the course of COPD in adults. A randomized trial of an improved chimney stove is currently under way in Guatemala, focusing on ALRI in children up to 18 months of age *(72)*. A cohort study in Kenya *(73)* describes significant exposure–response relationships for all acute respiratory infections, associated with the use of traditional and improved wood/charcoal stoves. A 16-year retrospective cohort study on lung cancer in rural China reported adjusted hazard ratios of 0.59 (95% CI 0.49–0.71) for men and 0.54 (95% CI 0.44–0.65) for women using improved coal stoves compared with traditional open coal fires *(74)*. Similar findings in the same cohort have recently been published for self-diagnosed COPD *(75)*.

Convincing scientific evidence for high exposure potentials in large populations, and emerging scientific evidence for associations with several health outcomes with high burdens of disease, point to an urgent need to initiate intervention programmes for indoor air pollution management within the larger framework of public health in developing countries. Although the selection of intervention options is deeply embedded in a matrix of environmental, health and economic considerations, it would be necessary for policy-makers to set appropriate risk reduction targets and optimize combinations of interventions that are most likely to allow these targets to be achieved.

Framework for air quality guidelines

The role of air quality guidelines in respect of indoor air pollution in developing countries should be the same as it is for air pollutants in other settings. Guidelines should encapsulate the best available evidence on health risks, and provide a basis for standard-setting by individual countries, agencies and others responsible for the development and implementation of policy to reduce risk. Nevertheless, the circumstances in which very large numbers of poor people are exposed to indoor air pollution are such that a pragmatic, somewhat non-traditional approach is needed, at least for the short to medium term. Waiting for science to produce the evidence for a numerical guideline value for indoor air pollutants in domestic settings in developing countries may result in the most vulnerable communities continuing to bear a large health burden for an indefinite period of time.

In Table 7, a framework for guidelines is proposed that: (*a*) recognizes the circumstances and practical difficulties in obtaining data on indoor air pollution; (*b*) suggests approaches to reducing risk together with feasible indicators for surveillance of air quality improvements; and (*c*) proposes a timescale over which transitions to acceptable air quality standards (similar to those that may be available in the developed world) are likely to take place. The guidelines are presented

Table 7. Framework for air quality guidelines for indoor air pollution in developing countries

Type of guideline	Timescale for application	Setting	Guideline level
Pragmatic	Immediate	Solid fuels are main household fuels	All homes to have stoves or other arrangements that vent smoke to the outside
		Transition to clean fuels such as LPG is gaining momentum	All homes to be using clean fuel for main cooking tasks (and if possible for heating where needed)
Intermediate	Immediate where some indoor air pollution data can be obtained; medium-term where no such data are currently likely to be available	Solid fuels still used extensively; several interventions involving improved stove design and/or cleaner fuels, shown to be well-accepted and effective (based on laboratory and community evaluations), are in large-scale use	Ranges of pollutant levels associated with different types of fuel, stove or other interventions
Traditional	Longer-term as more data and evidence on risk accrue and levels of pollution comparable with the developed world become achievable	Cleaner fuel use is more widespread, but not universal especially among poorer rural and urban homes	As for outdoor air pollution, or for indoor air in developed countries if guidelines become available

using a tiered approach. Different tiers may be used in parallel (for example, pragmatic guidelines nationally, using the census, complemented by ad hoc studies of indoor air pollution in selected communities). Nevertheless, they also represent a transition over time associated with socioeconomic development, greater use of clean fuels and improved stove technology, and growing technical capacity for air quality monitoring. A precedent for this type of pragmatic guideline setting is found in the water and sanitation field *(76)*. Although more detail on such "technology-based guidelines" for indoor air pollution may be desirable for giving practical guidance to policy-makers and others supporting implementation (key target groups for WHO air quality guidelines), additional applied research is needed before this can be specified. However, the framework in Table 7 should

Table 8. Burden of disease for Kenya, based on regional data for 2001

		Estimates of burden (DALYs lost)		
Disease	Group	Lower	Central	Upper
ALRI	Female	196 000	242 000	276 000
	Male	251 000	309 000	353 000
	Total	447 000	552 000	629 000
COPD	Female	9 780	12 400	14 900
	Male	0	9 900	16 700
	Total	9 780	22 300	31 600

How assessed	Application to standards
National censuses, other population sample surveys, ad hoc studies.	Realistic targets to be set for coverage (percentage of homes) to be increased over, for example, a 5–10-year period, as appropriate .
National censuses, other population sample surveys, ad hoc studies.	Realistic targets to be set for coverage (percentage of homes) to be increased over, for example, a 5–10-year period, as appropriate.
Ad hoc household studies to measure PM, carbon monoxide or other pollutants in the kitchen. In some cases, studies would also include personal exposure of cooks and young children or other vulnerable family members. Relatively few such studies in any given country can be expected in the short term, but should be encouraged as capacity is extended.	Guidelines would indicate the range of, for example, 24-hour average PM_{10} expected in a kitchen with an improved biomass stove with chimney. Levels high in the range would indicate poor design, condition or use, while levels low in the range would indicate a well-functioning device and appropriate use.
Ad hoc household studies, and in time and as measurement technology evolves as sub-studies, which are part of larger-scale sample surveys to measure PM, carbon monoxide or other pollutants in the kitchen. In some cases, studies would also include personal exposure of cooks and young children or other vulnerable family members.	The guidelines would be used to set standards to be achieved in all homes, as it becomes more realistic to do so, and when it becomes practical to monitor pollution in representative samples of homes on a periodic basis while patterns of fuel and stove use indicate that this remains a cost-effective component of risk-reduction strategies.

provide a basis for the further development of indicators and targets appropriate to national and local circumstances.

A valuable background activity that will serve to prioritize action on setting and implementing guidelines in a country is the calculation of national burden of disease from the use of solid fuels. An example for Kenya is shown in Table 8. Guidance on this is now available from WHO *(77)*. The method yields lower, central and upper estimates of disease burden, and will allow comparison with the burden resulting from other risk factors and diseases in the country. It is hoped that the air quality guidelines framework proposed in Table 7, together with the accompanying background information, will provide momentum for moving towards effective and widespread management of indoor air pollution in the developing world.

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Part 2

Risk assessment of selected pollutants

10. Particulate matter

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Introduction

Since the second edition of *Air quality guidelines for Europe* was issued in 2000 *(1)*, there has been an explosive growth in research relevant to the health effects of airborne PM. The evidence comes from a variety of research disciplines, including epidemiology, toxicology, exposure assessment and atmospheric sciences. The evidence obtained has deepened understanding of the risks posed to human health and to ecosystems by airborne particles, and also provided insights into the complexity of airborne particles and their myriad sources, along with the attendant implications for control. The scientific foundation for proposing air quality guidelines is far more substantial than in the past; the voluminous scope of available evidence, however, poses a challenge in developing guidelines, as the amount of evidence for a number of adverse health effects is now increasingly sufficient for this purpose but not easily summarized, either quantitatively or qualitatively. For some of the health outcomes, including increased risk of mortality on a short-term basis, dose–response relationships have been demonstrated at concentrations extending, at the lowest levels, well into the ranges measured at present in many cities in both developed and developing countries. The consequent inability to identify levels below which adverse effects are not anticipated implies that any standard may leave some residual risk unless concentrations are reduced to background levels.

A systematic review of this new evidence is beyond the scope of this chapter, which draws extensively from recent comprehensive syntheses and from the meta-analyses of time series studies carried out by Anderson et al. for WHO *(2)*. The full suite of evidence on PM was assembled by the US Environmental Protection Agency (USEPA) in its 2004 document *Air quality criteria for particulate matter (3)*. The related document, *Review of the national ambient air quality standards for particulate matter: policy assessment of scientific and technical information (4),* provides a distillation of the findings of the criteria document and policy implications. In 1998, the US National Research Council established its Committee on Research Priorities for Airborne Particulate Matter, which was charged with setting out an agenda for PM research and then tracking progress on this agenda *(5)*. In its fourth and final report, the Committee gauged progress on its research agenda, based on a process involving expert judgement and a systematic review. It also highlighted uncertainties in the evidence available on PM, across its framework that begins with sources of PM and ends with adverse effects

on health. Additionally, since 1997, the findings of major multi-city time series analyses have been published, including a series of papers from the Air Pollution and Health: A European Approach 2 (APHEA 2) team *(6–10)* and from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) *(11–15)*. The World Health Organization has also conducted a comprehensive review of the health effects of PM as part of the European Commission's Clean Air for Europe (CAFE) process. The health effects of ultrafine particles have also been reviewed *(16)*.

The authors of this chapter have relied primarily on these reports, supplementing their compilations with more recent publications as warranted by the contributions of new studies to reducing uncertainty. Quantitative summaries of the literature are based on published meta-analyses.

General description

Particle characteristics

PM in urban and non-urban environments is a complex mixture with components having diverse chemical and physical characteristics. Research on PM and the interpretation of research findings on exposure and risk are complicated by this heterogeneity, and the possibility that the potential of particles to cause injury varies with size and other physical characteristics, chemical composition and source(s). Different characteristics of PM may be relevant to different health effects. Newer research findings continue to highlight this complexity and the dynamic nature of airborne PM, as it is formed either primarily or secondarily and then continues to undergo chemical and physical transformation in the atmosphere.

Nonetheless, particles are still generally classified by their aerodynamic properties, because these determine transport and removal processes in the air and deposition sites and clearance pathways within the respiratory tract. The aerodynamic diameter is used as the summary indicator of particle size; the aerodynamic diameter corresponds to the size of a unit-density sphere with the same aerodynamic characteristics as the particle of interest. The differences in aerodynamic properties among particles are exploited by many particle sampling techniques.

For current regulatory purposes, PM has been classified by aerodynamic diameter, as size is a critical determinant of the likelihood and site of deposition within the respiratory tract and evidence has become available on the risk associated with specific size groups. Initially, regulations and guidelines were directed at very general measures of PM concentration, including total suspended particulate (TSP) matter in the United States and black smoke (BS) in Europe. In 1987, USEPA promulgated a standard for PM less than 10 μm in aerodynamic diameter (PM_{10}) *(17)* and then, in 1997, a standard for PM less than 2.5 μm in

aerodynamic diameter ($PM_{2.5}$) was added *(18)*. In WHO's 2000 air quality guidelines *(1)*, guidance was given in relation to both of these PM indicators. By definition, PM_{10} includes $PM_{2.5}$ and thoracic coarse mass PM (the difference between PM_{10} and $PM_{2.5}$ is often referred to as "coarse" mass PM). PM_{10} includes those inhalable particles that are sufficiently small to penetrate to the thoracic region; the fine fraction of PM_{10} is cut off from the coarse fraction at 2.5 μm in aerodynamic diameter ($PM_{2.5}$), a size fraction with a high probability of deposition in the smaller conducting airways and alveoli.

In urban atmospheres, PM can generally be separated into three major fractions on the basis of particle size: coarse particles larger than 2.5 μm in aerodynamic diameter, fine particles smaller than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and ultrafine particles, those smaller than 0.1 μm (100 nm). These size fractions differ in their overall contributions to airborne particle mass and in their origins, physical characteristics and chemical composition.

The largest particles, those in the coarse fraction or mode, are to a large extent mechanically produced by the break-up of larger solid particles. The amount of energy required to break these particles into smaller sizes increases as the size decreases. Biological sources may also contribute to this mode. Thus, in urban areas, the coarse particles typically contain resuspended dust from roads and industrial activities, and biological material such as pollen grains and bacterial fragments. The coarse particles also typically include the earth's crustal materials such as wind-blown dust from agricultural processes, uncovered soil, unpaved roads or mining operations. Traffic produces road dust and air turbulence that can re-entrain road dust near roadways. Near coasts, evaporation of sea spray can also produce large particles. Coarse particles may also be formed from the release of non-combustible materials in combustion processes, i.e. fly ash.

Smaller particles – those smaller than 2.5 μm in aerodynamic diameter and known as the fine fraction or mode – are largely formed from gases, but combustion processes may also generate primary particles in this size range. Typically these particles originate as ultrafine particles produced by nucleation–condensation of low-vapour-pressure substances formed by high-temperature vaporization or by chemical reactions in the atmosphere to form very small particles (nuclei). Particles in this nucleation range or mode subsequently grow by coagulation (the combination of two or more particles to form a larger particle) or by condensation of gas or vapour molecules on the surface of existing particles. Coagulation is most efficient for large numbers of particles, while condensation is most efficient for large surface areas. Thus the efficiency of both coagulation and condensation decreases as particle size increases, and this decreasing efficiency effectively results in an upper limit of approximately 1 μm that cannot be exceeded by particle growth other than by hygroscopic growth in humid atmospheres. Thus, particles tend to "accumulate" in a size range of 0.1–1 μm, the so-called "accumulation mode".

Submicrometre-sized particles can also be produced by the condensation of metals or organic compounds that are vaporized in high-temperature combustion processes, and by the condensation of gases that have been converted in atmospheric reactions to low-vapour-pressure substances. The main precursor gases are sulfur dioxide, nitrogen oxides, ammonia and volatile organic compounds. Consequently, changes in the atmospheric concentrations of these gases may affect ambient PM concentrations. For example, sulfur dioxide is oxidized in the atmosphere to form sulfuric acid (H_2SO_4). Nitrogen dioxide (NO_2) is oxidized to nitric acid (HNO_3), which in turn reacts with ammonia (NH_3) to form ammonium nitrate (NH_4NO_3). The particles produced by the intermediate reactions of gases in the atmosphere are called secondary particles. The fine fraction, therefore, is typically composed of nitrate, sulfate, ammonium, black (elemental) carbon, a large number of organic compounds and trace metals. This fraction also contains most of the acidity (hydrogen ion) of PM, although in fog some coarse acid droplets are also present *(19)*. Biomass smoke particles are smaller than 1 μm, with a peak in the size range of 0.15–0.4 μm *(20)*.

In 2003, a comprehensive report on airborne PM in Europe was compiled *(21)*. Sulfate and organic matter were found to be the two main contributors to the annual average PM_{10} and $PM_{2.5}$ mass concentrations, except at roadside monitoring sites where mineral dust (including trace elements) is also a main contributor to PM_{10}. On days when PM_{10} concentration exceeds 50 μg/m^3, nitrate becomes a major component of PM_{10} and $PM_{2.5}$. Black carbon contributed 5–10% to $PM_{2.5}$ and somewhat less to PM_{10} at all sites, including the natural background sites. Its contribution increases to 15–20% at some of the kerbside sites.

In North America, data on ambient PM concentrations and composition and its temporal and spatial distribution were recently summarized *(22)*. In general, PM_{10} mass includes 40–90% $PM_{2.5}$, the remainder being coarse PM. Annual average $PM_{2.5}$ concentrations above15 μg/m^3 were observed at locations in California and in many urban sites in the east and south-east of the United States. Twenty-four-hour average concentrations of $PM_{2.5}$ in Mexico City frequently exceeded 65 μg/m^3 and are among the highest measured in North America. Carbonaceous material is a major component of PM throughout North America, while sulfate comprises a high proportion (20–50%) of PM mass in eastern North America and ammonium nitrate is a major contributor (>25%) in California. In Mexico City, PM composition is dominated by organic and black carbon and ammonium sulfate, with smaller amounts of ammonium nitrate. In general, coastal regions experienced more seasonality in PM composition than was observed in interior regions. Maximum concentrations occurred during the summer in the east and during the autumn and winter in the western part of North America.

Ambient concentrations

In the past decade, numerous measurements of PM_{10} and $PM_{2.5}$ have been made in North America. Although annual average $PM_{2.5}$ concentrations can vary spatially by a factor of 2 within a 50–100-km area, three-year average mass concentrations exceeding 15 μg/m^3 were measured at 50% of American urban sites. Twenty-four-hour $PM_{2.5}$ averages exceeded 65 μg/m^3 for 2% of the time at many Californian sites and this level was occasionally exceeded at all south-eastern sites. In Canada, 24-hour averages above 30 μg/m^3 were measured for more than 2% of the year at most southern Ontario and Quebec locations. In Mexico City, 24-hour concentrations frequently exceeded 65 ug/m^3 *(22)*.

Data from a study conducted in 28 European locations in the winter of 1993–1994 indicated low PM_{10} concentrations in Northern Europe, with mean urban values of around 20 μg/m^3. Higher concentrations were found in areas with high population and traffic density such as Amsterdam and Berlin (45–50 μg/m^3) and central European cities such as Budapest (57 μg/m^3), and even higher concentrations occurred in southern European cities such as Pisa (61 μg/m^3) and Athens (98 μg/m^3). The comparability of measurement locations and procedures was ensured by detailed protocols, site visits and interlaboratory comparisons. Urban/rural contrasts within countries were often small to negligible, even at distances of up to 100 km, unless mountains or hills separated the urban from the rural locations, as in Greece *(23,24)*.

Although less information is available for locations outside North America and Europe, outdoor particle concentrations are currently highest in the cities of developing countries, particularly Asian cities with extensive coal burning *(25)*. For example, measurements from four Chinese cities made for the purpose of epidemiological studies indicated annual mean PM_{10} concentrations of 115–275 μg/m^3 in urban locations and 68–192 μg/m^3 in suburban locations in the same cities. $PM_{2.5}$ comprised 50–75% of the PM_{10} concentration *(26)*. In Bangkok, mean 24-hour PM_{10} concentrations of 80–100 μg/m^3 were measured in a series of panel studies *(27)*. The data on the very high PM concentrations in cities in developing countries in Asia have recently been summarized *(28)*.

Concentrations in cities in other parts of the world may also be high relative to North America and Europe, although data are sparse. For example, annual average PM_{10} concentrations in 17 Latin American and Caribbean cities ranged from 30 to 118 μg/m^3 (D. M. Maisonet, personal communication, 2005). For the WHO Comparative Risk Assessment, a combination of measurements and model-predicted PM concentrations was used to make estimates of exposure for inhabitants of more than 3200 cities with populations over 100 000 in 2000. Estimates of population-weighted annual mean concentrations of $PM_{2.5}$ ranged from 11.7 μg/m^3 in Western Pacific Region A to 52.8 μg/m^3 in Western Pacific Region B. Concentrations of PM_{10} ranged from 25.4 μg/m^3 in Americas A to 123 μg/m^3 in South-East Asia Region B. In the cities considered in the WHO estimates,

52% of the world's population was projected to be exposed to city-specific annual average PM_{10} concentrations above 50 μg/m^3, 27% to concentrations above 100 μg/ m^3, 8% to concentrations above 150 μg/m^3 and 2.5% to concentrations above 200 μg/m^3 *(29)*. Additional information on global PM concentrations is summarized in Chapter 2.

Measurements from south-east Asia indicate that particles are the main air pollutant during periods of air pollution from fires involving vegetation *(30)* and that very high concentrations may be experienced. For example, during a 2–3-month period in 1994, PM_{10} levels of up to 409 μg/m^3 were recorded in Kuala Lumpur *(31)* and of 36–285 μg/m^3 in Singapore *(32)*. In 1997, PM_{10} levels as high as 930 and 421 μg/m^3 were measured in Sarawak and Kuala Lumpur, respectively, while levels in Singapore and southern Thailand were somewhat lower *(33)*. Closer to the fire source in Indonesia, PM_{10} concentrations as high as 1800 μg/m^3 were measured *(34)*. A more limited vegetation fire episode affected regions of Borneo in February–May 1998, and PM_{10} levels as high as 440 μg/m^3 were measured in Brunei Darussalam during this period *(30)*.

Data on exposures to acidic aerosols in North America were summarized by Spengler et al. in 1990 *(35)*, showing peak daily hydrogen ion concentrations above 500 nmol/m^3. Annual average hydrogen ion measurements in 16 American and Canadian cities in north-eastern North America (1988–1991) were in the range of 19–52 nmol/m^3, while summertime means were 29–88 nmol/m^3 *(36)*. Levels of aerosol acidity measured in the Netherlands over the last 20 years were generally very low, but may not have been representative of Europe as a whole *(37–39)*.

Standardized measurement programmes for ultrafine particles have not yet been widely implemented, although several recent research programmes have conducted standardized measurements of particle number concentrations in several locations. In Europe, for example, measurements have been collected in five cities and show strong seasonal patterns and diurnal variability, with peak concentrations during periods of morning traffic *(40,41)*.

Large-scale changes in social and economic policies may have marked effects on the characteristics of particulate air pollution. For example, changes in particle size distribution were observed in the early 1990s after the unification of Germany. Kreyling and colleagues *(42)* observed large reductions in concentrations of TSP, PM_{10}, $PM_{2.5}$ (and sulfur dioxide), and increases in the number concentration of ultrafine particles, as the relative contribution to air pollution of heavy industry and power generation decreased and that of vehicular traffic increased.

Sources

There are numerous sources of particles related to human activities as well as natural sources. By measuring the temporal and spatial patterns of the chemical composition of particles in the air and combining this information with

meteorology, the particle mass can be apportioned to various sources. Methods for estimating the contributions of specific sources to PM concentrations have been reviewed in detail by Brook et al. *(43)* and Watson et al. *(44)*. Although specific source impacts differ between regions, combined analyses suggest that, in developed countries, more than two thirds of $PM_{2.5}$ mass is traceable to anthropogenic sources. Major source categories include the combustion of fossil fuels (electrical utilities and internal combustion engines), biomass burning (residential wood burning, wildfires and other biomass burning such as agricultural burning) and ammonia emissions from agricultural operations. For example, Hildemann et al. *(45)* showed that industrial-scale boilers, fireplaces, cars with and without catalytic converters, diesel trucks and meat-cooking operations emit particles primarily in the range 0.1–0.2 μm. Petrol-fuelled cars with catalytic converters emitted a much lower particle mass than those without converters, while diesel trucks emitted about 100 times the particle mass, per kilometre driven, of a passenger car with a catalytic converter. Diesel PM is almost pure carbon and has the form of submicrometre-sized aggregates of ultrafine carbon spheroids with aerodynamic diameters of around 0.1 μm.

Regional apportionment of ambient PM mass is a common approach to air quality management. Vickery *(46)*describes major source contributions in nine different regions of North America. Chow et al. *(47)*, for example, estimated the annual average source contributions for six sites in the California San Joaquin Valley to $PM_{2.5}$ and PM_{10}. Secondary ammonium sulfate, secondary ammonium nitrate and motor vehicle exhausts were found to be major contributors to $PM_{2.5}$, explaining 50–70% of the mass. About 40–60% of the coarse particles were found to originate from geological contributions (fugitive dust from tilling, roadways and construction). A similar study conducted in São Paolo *(48)* showed that emissions from residual oil and diesel fuel combustion (41%) and resuspended soil dust (28%) contributed most to $PM_{2.5}$. Soil dust (59%) and industrial emissions (19%) contributed most to the coarse fraction (2.5–15 μm). In Europe, Querol and colleagues *(49)* assessed source contributions to PM_{10} and $PM_{2.5}$ at regional background and roadside locations in seven regions. At urban sites, carbonaceous aerosols and secondary inorganics were major contributors to $PM_{2.5}$ and, to a slightly lesser extent, PM_{10} mass. At roadside sites there was a substantial contribution of resuspended dust to $PM_{2.5}$. Querol and colleagues estimated the natural contributions to PM_{10} and $PM_{2.5}$ concentrations across a range of European locations to be in the order of 4–8 $\mu g/m^3$ and 1–2 $\mu g/m^3$, respectively.

Only a few source apportionment studies of PM have been carried out in developing countries. Begum et al. *(50)* assessed PM sources at a roadside location in Dhaka, Bangladesh. Approximately 50% of the PM ($PM_{2.2}$) mass was attributed to motor vehicles, including two-stroke vehicles. Four per cent of the PM mass was resuspended lead, even though lead had been eliminated from petrol in Bangladesh several years earlier. Soil dust was the largest component of the

coarse particle fraction ($PM_{2.2–10}$), accounting for 50–70% of the total coarse mass. Biomass smoke is also a major contributor to ambient PM concentrations in cities in developing countries, contributing, for example, 12–50% of the $PM_{2.5}$ in Rahjshahi, Bangladesh *(51)*.

In many parts of the world, vegetation fires are major sources of ambient particles. During such episodes, PM is the air pollutant most consistently elevated in areas affected by fire smoke *(52)*. For example, during fires in southern California, Phuleria and colleagues measured PM_{10} concentrations 3–4 times higher than normal, while particle numbers and carbon monoxide and nitric oxide concentrations were higher by a factor of two and concentrations of nitrogen dioxide and ozone were essentially unchanged *(53)*. Further, as biomass combustion emissions can be transported over hundreds of kilometres *(52,54)*, many of the gaseous species are converted to particles during transport. Reinhardt, Ottmar & Castilla *(55)* measured respirable particle ($PM_{3.5}$) concentrations 5–10 times higher than background levels in a rural area of Rondonia, Brazil during the peak of the biomass burning season in 1996. Mean levels of 190 $\mu g/m^3$ and levels as high as 250 $\mu g/m^3$ were measured during several of the 12-hour sampling periods. Additional studies of fine particle composition associated with biomass burning in the Amazon Basin were reported by Artaxo et al. *(56)*, who found 24-hour average PM_{10} and $PM_{2.5}$ mass concentrations as high as 700 and 400 $\mu g/m^3$, respectively.

A number of chemicals are enriched in wood smoke relative to other sources of air pollution. Examples include potassium, methoxyphenols, levoglucosan, retene and specific resin acids (e.g. abietic acid) *(57–59)*. Detailed analysis of organic wood smoke aerosol were conducted by Rogge et al., who measured nearly 200 distinct organic compounds, many of them derivatives of wood polymers and resins *(60)*.

Measurement methods

The availability of methods to accurately measure various size fractions of PM is critical to the development of standards. At present, PM monitoring throughout the world is extremely limited and there is a great need for more measurements outside North America and Europe. In the recent WHO Comparative Risk Assessment project, only a limited number of PM measurements, primarily of PM_{10}, were available globally. Annual average concentrations were available for only 216 cities of a total of 3400 cities with populations of more than 100 000, mostly in Europe and North America. In the locations with monitoring data, a model based on population density, the intensity of local economic activity, per capital fuel use, per capita income, and meteorological and topographical indicators was developed and explained 88% of the variability in PM. This model was then applied to 3200 cities without measurement data to generate estimates of PM_{10} concentrations *(29)*. Alternative methods based on remote sensing or visibility data have also been used to estimate PM concentrations *(61)*.

Methods for sampling and analysing airborne PM have been discussed by WHO *(62)* and USEPA *(3)* and are reviewed by McMurry et al. *(22)*. Early methods include BS measurement, the darkness of a stain obtained on a white filter-paper though which air has been passed (according to the British smoke method, sometimes referred to as the BS method) and also TSP measurement, which captured particles of all sizes. Methods for measuring TSP (by high-volume sampler) were used extensively in the United States until the late 1980s. However, the size range sampled extends at its upper end well beyond those particles that can penetrate into the thorax and, in arid regions, the method is liable to sample wind-entrained soil dust of large aerodynamic diameter. Accordingly, in many countries, PM with a median size cut-off point of 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$) aerodynamic diameter is the indicator for air quality standards.

Frequently used measurement methods at present include continuous PM monitors such as the tapered elemental oscillating microbalance and the β-attenuation sampler, and filter-based samplers such as the dichotomous sampler, or any of the USEPA-designated $PM_{2.5}$ samplers *(22,63)*. Measurements of coarse-mode PM can be made directly by a dichotomous sampler, but coarse-mode PM mass can also be inferred by subtracting measured $PM_{2.5}$ concentrations from measured PM_{10} concentrations. Such calculations, however, incorporate measurement error that is compounded by making a calculation involving two measurements. This underscores the need for standardized measurement methods and criteria for the siting of monitors.

Increasingly, sites are being established for the continuous measurement of PM components such as organic and black carbon, sulfate, nitrate and ammonium. Further, routine measurements of particle number concentrations (ultrafine particles) are now possible *(22)*. Numerous compact, quiet, continuous and low-volume filter-based methods are also available and applicable to indoor and personal monitoring of PM exposure *(64)*.

As the physical and chemical composition of airborne PM varies in time and space, the various measures of airborne PM can only be compared approximately to each other. Consequently, there is uncertainty in comparing data from different countries. The conversion of BS measurement data to PM_{10} concentration is particularly uncertain; the uncertainty arises from the completely different principles of measurement and the large temporal and geographical variation of the contribution of "black" material to thoracic airborne PM mass. Measurements from 28 European locations in the winter of 1993/1994 with co-located measurements of BS and PM_{10} indicate location-specific BS : PM_{10} ratios varying from less than 0.3 to about 1.4, with most of the measurements giving ratios well below unity *(24)* . Data from the American–Canadian 24-Cities Study have shown ratios of fine particles (2.1 μm aerodynamic diameter) to PM_{10} varying from 0.30 to 0.70 depending on location, with the higher ratios generally observed in the eastern states and provinces *(65)*. Overall, typical ratios of 0.5–0.8 are found in urban

areas in North America and Europe *(3,66)*, with ratios closer to 0.5 in urban areas in developing countries *(67,68)*.

"Black smoke" (BS) refers to a measurement method that uses the light reflectance of particles collected on filters to assess the "blackness" of the collected material. The method was originally developed to measure smoke from coal combustion and a calibration curve exists, developed in the 1960s, that translates the reflectance units into a mass number. That translation is no longer valid, as was shown in a Europe-wide study conducted in the winter of 1993/1994 *(24)*. However, measurement of the light reflectance of PM filters has been shown to be highly correlated with elemental carbon in some recent studies *(69,70)*.

In a number of locations, vehicular traffic has been shown to be an important source of ultrafine particles and very high number concentrations have been observed near busy roads, with steep gradients in concentration at distances increasing up to several hundred metres from such roads *(71–73)*. It should be noted that ultrafine particles are inherently unstable in the atmosphere because they coagulate quickly. Exposure assessment based on single ambient monitoring stations is therefore more subject to error than it is for PM mass.

Exposures

There is a substantial new literature on exposure of the general population, including healthy persons and those with diseases considered to place them at increased risk from exposure to particles (Table 1). These studies have been carried out primarily in the United States and Europe. Since humans in developed countries spend much more time indoors than outdoors, information is needed on the extent to which outdoor particles (particles of ambient origin) penetrate into homes and other indoor spaces. This information is needed for interpreting the epidemiological studies that have used outdoor levels of particles as a primary exposure measure and for the development of control strategies. While numerous studies have demonstrated that indoor particle concentrations, as well as personal exposures, are usually higher than corresponding outdoor levels, there is currently little evidence to suggest adverse health impacts associated with non-ambient particles (those of indoor origin), with the important exception of particles arising from smoking and other combustion processes and of selected biological agents. The higher indoor levels in part reflect indoor sources such as smoking and cooking and also human activities that generate and resuspend particles, creating a "personal cloud" of particles *(74,75)*.

In one representative study in a developed country setting, Clayton et al. *(76)* conducted a large-scale study of indoor and outdoor PM_{10} and $PM_{2.5}$ concentrations in California. Personal exposure to PM_{10} was also measured in a population of over 100, including smokers and nonsmokers. Personal concentrations were found to exceed indoor as well as outdoor concentrations by a factor of about 1.5, although this analysis did not distinguish between ambient and non-ambient

Table 1. Summary measures of selected personal particle exposure monitoring studies

Study population	N [a]	Exposure metric	Mean personal ($\mu g/m^3$)	Mean ambient ($\mu g/m^3$)	Median personal–ambient correlation (r) [b]	Reference
Adults with pre-existing disease						
Adult COPD patients in Vancouver	16 x 7	$PM_{2.5}$	18.2	11.4	0.48	Ebelt et al. *(82)*
Adult COPD patients in Seattle	34 x 10	$PM_{2.5}$	10.5	10.1	0.37 [c]	Liu et al. *(83)*
Adult CVD patients in Seattle	27 x 10	$PM_{2.5}$	10.8	10.1	0.37 [c]	Liu et al. *(83)*
Adult COPD patients in Boston	18 x 12	$PM_{2.5}$	21.6	14.2 [d]	0.61	Rojas-Bracho, Suh & Koutrakis *(84)*
Adult CVD patients in Amsterdam	36 x 22	$PM_{2.5}$	24.3	20.6	0.79	Janssen et al. *(70)*
Adult CVD patients in Helsinki	46 x 27	$PM_{2.5}$	10.8	12.6	0.76	Janssen et al. *(70)*
Adult COPD patients in Vancouver	16 x 7	SO_4^{2-}	1.5	1.9	0.96	Ebelt et al. *(82)*
Adult COPD patients in Boston	17 x 8	PM_{10}	37.2	22.2 [d]	0.35	Rojas-Bracho, Suh & Koutrakis *(84)*
Adult COPD patients in Boston	17 x 8	$PM_{10-2.5}$	15.6	8.1 [d]	0.30	Rojas-Bracho, Suh & Koutrakis *(84)*
Older adults						
Elderly adults in Seattle	28 x 10	$PM_{2.5}$	9.3	10.1	0.47 [c]	Liu et al. *(83)*
Elderly retirement home residents in Baltimore	21 x 15	$PM_{2.5}$	13.0	22.0	0.80	Williams et al. *(85,86)*
Elderly retirees in Baltimore	10 x 22	$PM_{2.5}$	12.8	21.0 [d]	0.82	Landis et al. *(87)*
Elderly retirees in Baltimore	15 x 12 Summer	$PM_{2.5}$	26.7	25.2	0.76	Sarnat, Koutrakis & Suh *(88)*
Elderly retirees in Baltimore	15 x 12 Winter	$PM_{2.5}$	18.5	5.6	0.25	Sarnat, Koutrakis & Suh *(88)*
Elderly retirees in Baltimore	15 x 12 Summer	SO_4^{2-}	5.6	10.5	0.88	Sarnat, Koutrakis & Suh *(88)*
Elderly retirees in Baltimore	15 x 12 Winter	SO_4^{2-}	2.1	1.0	0.72	Sarnat, Koutrakis & Suh *(88)*
Elderly retirees in Baltimore	10 x 22	SO_4^{2-}	4.5	10.2 [d]	0.95	Landis et al. *(87)*
Adults (50–70 years) in the Netherlands	37 x 7	PM_{10}	61.7	41.5	0.50 (0.71) [e]	Janssen et al. *(89)*

▶

Study population	N [a]	Exposure metric	Mean personal ($\mu g/m^3$)	Mean ambient ($\mu g/m^3$)	Median personal–ambient correlation (r) [b]	Reference
▶ Elderly retirees in Baltimore	15 x 12 summer	PM_{10}	33.9	34.0	0.64	Sarnat, Koutrakis & Suh *(88)*
Elderly retirees in Baltimore	15 x 12 winter	PM_{10}	28.0	7.2	0.53	Sarnat, Koutrakis & Suh *(88)*
Elderly retirees in Baltimore	15 x 12 summer	$PM_{10-2.5}$	7.2	8.4	0.11	Sarnat, Koutrakis & Suh *(88)*
Elderly retirees in Baltimore	15 x 12 winter	$PM_{10-2.5}$	9.6	–1.3	0.32	Sarnat, Koutrakis & Suh *(88)*
Children						
Asthmatic children in Seattle	19 x 10	$PM_{2.5}$	13.3	10.1	0.30 [c]	Liu et al. *(83)*
Children (non-smoking parents) in the Netherlands	9 x 7	$PM_{2.5}$	24.4	17.1	0.92	Janssen et al. *(90)*
Children (non-smoking parents) in the Netherlands	16 x 7	PM_{10}	84.0	38.5	0.63	Janssen et al. *(91)*

[a] Number of subjects x (nominal) number of repeat measurements.
[b] Median of individual correlations of particle exposure studies with multiple measurements per person.
[c] Estimated from figure.
[d] Refers to residential outdoor and not central-site measurement.
[e] After excluding ETS exposure.

particles. Personal exposure studies have also provided insight into the determinants of PM exposure. For example, studies have shown that ambient particles are responsible for approximately 50% of total $PM_{2.5}$ exposure; indoor concentrations of PM of ambient origin are largely determined by the air exchange characteristics of the indoor environment and, on average, indoor concentrations of $PM_{2.5}$ of ambient origin are 40–70% of ambient $PM_{2.5}$ concentrations *(77–79)*. Estimates of exposure to the ambient component of PM have been applied in several epidemiological studies; the results indicate that use of this specific estimate of exposure enhances sensitivity for detecting associations with health outcomes *(79–81)*.

Although the majority of published studies on particle exposure have been conducted in developed countries, global total population exposure to PM is dominated by indoor exposures to solid fuels (coal and biomass) in developing countries *(92)*. In developing countries, extremely high indoor exposures may occur as a result of cooking with biomass fuels. Smith et al. *(93)* compiled findings from developing countries on PM exposure in homes resulting from the use of biomass fuel. During cooking, concentrations are in the mg/m^3 range, 1–2 orders of magnitude higher than fine particle concentrations measured in urban

ambient air. The monitoring data indicate that some of the highest exposures to $PM_{2.5}$ are typically experienced in this setting *(25)*.

While personal exposures to PM and its components are influenced by indoor sources such as smoking and cooking, in addition to outdoor sources, there is a clear correlation at the population level between ambient PM concentrations and concentrations of personal exposure to PM of ambient origin over time, especially for fine combustion particles. On a population level, concentrations of personal PM exposure "track" ambient PM concentrations over time, although the actual levels may differ. Thus, measurements of PM in ambient air can serve as a reasonable proxy for personal exposure in time series studies based on short-term changes in ambient levels.

In short-term studies, the relationship between ambient concentrations and personal PM exposures has been studied in numerous locations (Table 1). The longitudinal correlation between ambient and personal PM varies from person to person, depending on factors such as exposure to environmental tobacco smoke and cooking emissions, and the infiltration characteristics of the home *(77,82,94)*. At the population level, however, the correlation between ambient concentrations and personal PM exposure over time is fairly high, supporting the use of ambient PM measurements in time series studies as an exposure indicator reflective of day-to-day variation *(70,84–86,89,91,94)*. Also, the correlations with ambient concentrations increase if PM constituents with few indoor sources, such as BS or sulfates, are used as indicators *(70,82,95)*.

While few studies have directly addressed whether ambient long-term PM concentrations are correlated with long-term personal PM exposure *(96)*, it is again important to distinguish between exposures to ambient and non-ambient particles. Studies of long-term exposure pose the difficult logistical problem of measuring personal PM exposure over long periods of time. Nonetheless, several relevant studies can be cited. Analyses conducted of EXPOLIS study data have suggested that long-term ambient PM concentrations are well-correlated with the population average of a series of personal $PM_{2.5}$ exposure measurements *(64)*. Early work from the Six Cities Study has shown that personal sulfate measurements conducted in Watertown (low ambient sulfate) were much lower than those conducted in Steubenville (high ambient sulfate) *(97)*. This finding supported the use of outdoor measurements as a personal exposure metric in this long-term study *(97)*.

Within-city spatial variability in PM concentrations and in concentrations of specific PM components has also been demonstrated *(98,99)*. This variability in ambient concentrations has also been reflected in variability in exposures between those residing in the urban core vs those residing on the outskirts of the city *(96,100)*.

Recent evidence has shown that exposures of people living near busy roads are insufficiently characterized by air pollution measurements obtained from urban

background locations *(101–103)*. In some cities, a significant part of the urban population may be affected by roadway sources. Roemer & van Wijnen *(101)* estimated that 10% of the population of Amsterdam was living along roads with more than 10 000 vehicles a day. In some urban areas, elevated exposures may particularly affect socially disadvantaged groups *(104)*. For example, in California socially disadvantaged children have a higher probability of living close to major roads than children who are not disadvantaged *(105)*.

Because commuting times are increasing in much of the world, exposures to particles inside vehicles are increasingly important contributors to total PM exposure. Depending on the other vehicles on the road, in-vehicle concentrations are typically 5–10 times higher than roadside and ambient background concentrations *(94,106,107)*.

Some studies have addressed exposures of susceptible populations, including children and people with chronic heart and lung disease (Table 1). For such persons, time–activity patterns may differ from those of healthy adults; for example, schools are obviously an important location of exposure (microenvironment) for children but not for adults generally. As with other outdoor air pollutants, children may also be exposed to a greater extent than adults because of their greater physical activity and likelihood that they spend a larger part of the day outdoors. Exposure–dose relationships may also differ for susceptible compared with nonsusceptible groups because of underlying lung disease or ventilatory patterns. The higher minute ventilation of children per unit mass increases the internal dose of pollutant for a given ambient concentration. Athletes and others exercising outdoors may also experience increased exposures owing to increased minute ventilation, and persons with underlying lung disease tend to have a more central pattern of deposition of inhaled PM.

Summary

There are now substantial data available on the sources and composition of PM and on personal exposures to particles of various population groups. The information shows the complex characteristics of PM as the mixture varies spatially and temporally. The mass-based standards that have been proposed inherently assume that all airborne PM has the same potential to cause adverse health effects, regardless of chemical composition or physical characteristics. While both observational and experimental findings imply that particle characteristics are determinants of toxicity, definitive links between specific characteristics and the risk of various adverse health effects have yet to be identified *(4,108)*. Consequently, this review and the proposed guidelines address PM mass in general as the indicator for consideration.

Mechanisms of toxicity

Introduction

Evidence from toxicological studies on PM provides critical information for establishing guidelines. Toxicological evidence is complementary to the observational findings of epidemiological studies, providing the framework for assessing the biological plausibility of observed associations. Studies designed to address the dose–response relationships can also inform the interpretation of exposure–response modelling of epidemiological data. Much toxicological research is now directed at identifying those characteristics of PM that determine toxicity, so that the most important PM sources for control can be identified.

As noted earlier, particles in inhaled air are deposited selectively throughout the respiratory tract at locations determined primarily by their size. Numerous sources of evidence show that inhaled particles have adverse consequences for the lungs and other organs. The evidence spans such diverse exposures as those occurring in occupational environments (e.g. silica and asbestos), in indoor environments (e.g. combustion particles from burning cigarettes and cooking) and in outdoor environments (e.g. particles from mobile and stationary sources).

Controlled exposure studies of humans and animals have shown that ambient PM or surrogate compounds, used to represent particles having particular characteristics, may have direct effects on the respiratory tract. These effects have mainly involved production of an inflammatory response, exacerbation of existing airway disease (e.g. hyperreactivity) or impairment of pulmonary defence mechanisms. Inhaled PM may increase the production of antigen-specific immunoglobulins, alter airway reactivity to antigens or affect the ability of the lungs to handle bacteria, suggesting that exposure may result in enhanced susceptibility to microbial infection *(109)*.

Inflammation is considered central to producing many of the health effects attributed to PM. Inflammation can be produced by oxidative stress via redox-sensitive transcription factors such as NF-κB, and numerous studies have demonstrated the ability of PM and surrogates to cause oxidative stress *(110)*. In addition, a neurogenic mechanism has been suggested that might be mediated by C-reactive fibres and histamine *(111,112)*. The expected cascade of molecular events has been demonstrated with PM exposure, including antioxidant depletion, NF-κB and AP-1 activation, Ca^{++} flux, kinase activation, phosphorylation of signalling molecules, gene expression and translation into protein of pro-inflammatory cytokines and chemokines such as IL-8 and TNFα *(110,113)*. In persons who are allergic, mechanisms related to the underlying disease process might also be relevant. Enhanced effects of PM are seen in asthmatics and allergic inflammation could be influenced by particles, as has been documented in animal models of inflammation *(114–116)*.

Other mechanisms are probably relevant for other consequences of PM exposure. Genotoxic events underlie the carcinogenic effects of particles. Both direct, particle-mediated genotoxicity *(117,118)* and indirect genotoxic effects of inflammatory cells from particle-exposed animals *(119)* have been described. As to cardiovascular outcomes, endothelial cells exposed to PM_{10} show changes indicative of enhancement of the potential for the endothelium to cause thrombosis *(120)*.

The respiratory tract is the portal of entry for inhaled particles and, consequently, clinical or subclinical effects in the respiratory tract may be reflected in subsequent events in other systems, or particles may be translocated outside of the respiratory tract without producing any observable pulmonary response. One potential pathway for extrapulmonary effects of PM is via systemic transport of cytokines produced in the lungs during an inflammatory response *(121)*. Another potential pathway is through effects on coagulation properties that lead to increased risk of stroke or myocardial infarction *(122)*. PM may also result in endothelial and general vascular dysfunction *(123)* and chronic exposure may increase the progression of atherosclerosis *(124)*. There is also the possibility that PM may have a direct effect on the heart, potentially through uptake of particles into the blood or through release of chemical components from PM into the circulation that affect either cardiac function or autonomic control of the cardiovascular system. Regarding the latter mechanism, both parasympathetic and sympathetic pathways are involved in cardiac function; stimulation of either of these by specific components of PM could affect blood pressure, heart rate and/or heart rate variability.

Diverse properties of PM may be relevant to effects of exposure on public health. There is thus a potentially large and complex matrix for experimental investigation that is defined by particle characteristics and adverse health effects. The following sections provide an overview of the relationship of the characteristics of PM with toxicity, addressing the biological plausibility for particular characteristics to be linked to specific toxic effects. This evidence is critical in determining whether standards for PM should incorporate PM mass overall as the indicator or should have more specific, compositional elements as well. Mass-based standards implicitly assume that all particles have the same toxicity, regardless of composition.

One difficulty in attempting to assess properties of particles that determine their relative toxicities is that observed biological outcomes following exposure often differ between different controlled exposure studies. These differences may arise from different endpoints and exposure concentrations and the use of different biological models, and from exposures to particles that were not comparable because of the manner in which the particles were generated, collected or used *(125)*. Effects on a specific biological endpoint may differ with exposures to particles having different characteristics, and some specific types of particle may affect some endpoints but not others *(126)*.

The toxicity of PM may potentially arise from the particle's presence on biological tissue, to the actions of its chemical constituents, including adsorbed components, or to some combination of these factors. Toxicological research has examined a number of physicochemical characteristics of PM in relation to its potential to produce adverse biological effects. In its final report, the US National Research Council's Committee on Research Priorities for Airborne Particulate Matter *(108)* provided a summary table of particle characteristics that may be important to health responses, including size mode, mass concentration, number concentration, acidity, particle surface chemistry, particle core chemistry, metals, carbon (organic carbon and black or elemental carbon), biogenic origin, secondary inorganic aerosols, and material associated with the earth's crust. Other characteristics that have been recognized as potentially playing a role in toxicity are particle surface area, chemical reactivity, water solubility of constituent chemicals and the geometric form of the particles. This listing, of course, is based on those characteristics that have undergone the most scrutiny by investigators in the field. Another relevant body of toxicological evidence comes from studies that have involved both animals and humans, using concentrated ambient particles (CAPs). This approach provides an opportunity to study ambient PM and to explore potential interactions among PM components or of PM components with gases. The human studies using CAPs are reviewed in the subsequent section. The animal studies provide limited evidence suggesting that high concentrations/doses of inhaled or instilled particles can exert cardiovascular-related systemic effects, but many of the studies provide conflicting evidence, especially with regard to heart rate, heart rate variability or other ECG markers of cardiac function. The group at New York University has reported a series of studies involving 5–6 months of daily exposure of mice to CAPs *(127–135)*. These studies offer the opportunity to explore mechanisms underlying the cumulative cardiovascular and nervous system effects seen in people.

Plausibility of human effects in relation to toxicological evidence

Epidemiological and clinical studies have linked PM to a range of health outcomes. The following adverse effects have been identified in relation to PM or specific PM components in a variety of types of study, from chamber studies to large-scale epidemiological analyses of acute effects in time series studies and of chronic effects in cohort studies:

- mortality and hospital admission in COPD patients *(136)*
- exacerbation of symptoms and increased use of therapy in asthma *(137)*
- mortality and hospital admission in cardiovascular disease patients *(138)*
- mortality and hospital admission in diabetes mellitus *(139)*
- increased risk for myocardial infarction *(122)*
- lung inflammation *(140)*
- systemic inflammation *(121)*

- endothelial and vascular dysfunction *(123,141)*
- development of atherosclerosis *(124)*
- increased incidence of infection *(109)*
- respiratory cancer *(142)*.

Evidence related to underlying mechanisms and the plausibility of these effects comes from a range of animal, cell and acellular models. Compared to cell and acellular models, studies on animals, particularly animal models of disease susceptibility, generally provide the most reliable and relevant evidence for extrapolation to man; studies involving in vitro models can provide insight into basic mechanisms. These models have well-known limitations, such as their necessary simplicity, species differences, high dose and dose rate in many studies (e.g. administration of PM by instillation), and the lack of models of subchronic or chronic exposure. These well-known shortcomings are not critically and specifically discussed here because of limitations of space. With regard to the specific health outcomes listed above in relation to human studies, relevant toxicological evidence is briefly reviewed below.

Mortality and hospital admission in COPD patients

There are no fully satisfactory animal models of COPD for use in air pollution research. COPD is characterized by airway inflammation, and experimental airway inflammation has served as the basis of several studies aimed at elucidating the PM/COPD interaction. Some studies have examined the effect of concomitant inflammation on the response to particles and shown susceptibility to PM *(143)*. Morphometry of the airways was examined in a study in nonsmokers from Vancouver (low PM) and Mexico City (high PM) *(144)*. The results showed relatively normal membranous and terminal bronchioles in Vancouver residents but thickened, fibrotic small airways in the Mexico City residents. The authors concluded that living in an area with high PM levels could lead to chronic airflow obstruction through airway remodelling that mimicked that aspect of COPD. PM exposure has been shown to cause inflammation and pro-inflammatory effects in numerous in vivo and in vitro studies (see below) and this inflammation would be expected to contribute to adverse effects in COPD. COPD is well-known to be associated with oxidative stress *(145)*, which is likely to be affected by the documented oxidative stress posed by PM *(110)*.

Exacerbation of symptoms and increased use of therapy in asthma

Asthma is an inflammatory condition of the airways, and the oxidative stress due to PM could increase the level of inflammation. Studies show greater sensitization to model antigens in PM-exposed rats *(137,146)*.

Mortality and hospital admission in cardiovascular disease patients

Numerous studies have shown alterations in blood pressure, heart rate and autonomic regulation of heart rate variability and also dysrhythmias that support the plausibility of adverse effects of PM on cardiovascular mortality and morbidity (see below) *(147–149)*. In addition, studies with rat models have shown increased oxidative stress on the heart *(150,151)* and evidence of myocardial degeneration, inflammation and fibrosis in heart muscle *(152)* following particle exposure.

Mortality and hospital admission in diabetes mellitus

Animal or other relevant studies have not been reported.

Increased risk for myocardial infarction

Several studies have used animal models of ischemic heart disease and have demonstrated worsening of the conditions predisposing to myocardial infarction after particle exposure *(153,154)*.

Lung inflammation

Numerous studies have demonstrated pulmonary inflammation following inhalation of CAPs *(155)* or instillation *(156,157)* of PM samples in a number of species.

Systemic inflammation

Evidence of systemic inflammation has been detected in the blood following exposure to a range of different particle types. Markers studied include fibrinogen *(158)*, leukocytosis *(159,160)* and bone marrow stimulation *(159)*.

Endothelial and vascular dysfunction

Endothelial dysfunction has been noted in rats exposed to particles, as shown by direct visualization of arterial dilatation of the spinotrapezius muscle in response to SNP *(161)* and endothelin *(162)*.

Development of atherothrombosis

Watanabe heritable hyperlipidaemic rabbits were exposed to PM_{10} by pulmonary instillation. Exposure to PM_{10} caused progression of atherosclerotic lesions compared to controls, as measured by the volume fraction of the coronary atherosclerotic lesions, plaque cell turnover and extracellular lipid pools in coronary and aortic lesions *(163)*. ApoE mice susceptible to development of atherosclerotic lesions were used in subchronic inhalation studies by Chen and colleagues *(130)*.[1]

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[1] Following the preparation of this chapter, two additional studies reported effects of subchronic exposure to particulate air pollution on the progression of atherosclerosis in animal experiments at levels close to current United States and European air quality standards *(164,165)*.

Subchronic exposure to CAPs had a significant impact on the size and composition of aortic plaques and vascular inflammation and accelerated plaque progression. Instillation of diesel exhaust particles in the tracheas of hamsters activates platelets and increases the size of experimentally induced thrombi *(111,166)*. Platelets from animals exposed to particles have shown activation, one of the first steps in the clotting cascade *(167)*.

Increased incidence of infection

Several studies have identified increased susceptibility to infection in animals exposed to particles and metals *(168,169)*.

Respiratory cancer

Animal studies have been carried out to address the carcinogenicity of specific types of particle, e.g. diesel particles, but not ambient PM generally. The diesel studies have been comprehensively reviewed by Cohen & Nikula *(170)*.

Evidence for specific PM characteristics in determining toxicity

Particle size mode as a modulator of PM toxicity

Evaluation of size mode alone as a modulating factor in PM toxicity is difficult since it is not independent of chemical composition, i.e. certain size modes tend to contain certain chemical components, such as metals in the fine mode and crustal materials in the coarse mode. Furthermore, there are clear differences between particles in different size modes in terms of total and regional dosimetry within the respiratory tract, and subsequent pathways and rates of translocation both within and outside of the respiratory tract. Thus, the consequences of differing dosimetry may not be readily separable from those of differing characteristics. For example, in a study using different size modes of the same chemical material, the adverse effects of ultrafine and fine particles were comparable when assessed in terms of deposition doses; however, since the deposition efficiency of the ultrafine particles was higher, their toxicity may actually have been greater than that for the fine particles when considering mass concentration as the exposure metric *(171)*. As another example of the importance of specific exposure metric in relation to response, in an in vitro study *(172)*, effects on one endpoint were found to be greater for fine particles than for coarse particles delivered at equal mass concentrations, but there was no difference in response when exposure data were expressed in terms of PM surface per volume unit of suspension.

Particle-size-dependent effects independent of chemical composition address the issue of a "nonspecific effect" of PM exposure, i.e. whether any biological effect of exposure is due merely to the particle's presence rather than to its specific chemistry. Unfortunately, this question cannot be answered unequivocally at present. For example, some studies have indicated that the enhancement of lipopolysaccharide-related lung injury by diesel exhaust particulate could be

attributed solely to the carbonaceous core of the particle, and not to any washed leachate or organic compound extract associated with the particle *(173,174)*. In some studies, however, the coarse and fine fractions of PM were equally effective in producing release of inflammatory mediators, and the effects were greater than those produced by carbon black, suggesting that chemicals adsorbed on to the particle surface, rather than the mere presence of the particle itself, were responsible for toxicity *(175)*.

The difficulty of assessing the relative roles of size and chemistry is quite evident from studies using CAPs. For example, in vitro exposures of cells to concentrated ambient coarse and fine particles from air in Southern California resulted in different levels of oxidative stress response; the response was related to specific chemical components that differed in relative concentration within each fraction *(176)*. Similarly, using CAPs from ambient air in Los Angeles, there appeared to be enhanced toxicity of ultrafine compared to fine particles in terms of generating redox activity, which was correlated with the organic carbon and PAH composition of these two size modes *(177)*.

For ultrafine particles, size itself rather than chemical composition may determine toxicity. Ultrafine particles appear to produce a more significant pulmonary inflammatory response than that produced by fine particles having the same chemical composition and at the same exposure mass concentration *(178–181)*. However, since for a given mass concentration an atmosphere consisting of ultrafine particles will have a greater number concentration than one consisting of fine particles, as well as a greater total surface area available for adsorption of toxic chemicals, exposure dose would actually be greater for ultrafine than for fine particles compared with other exposure metrics.

Any enhanced biological effect from ultrafine particles may go beyond pulmonary inflammation, and may be relevant to systemic health outcomes found in epidemiological studies. For example, rats exposed to ultrafine carbon showed no evidence of pulmonary inflammatory response but did show extrapulmonary effects, including changes in the number of blood neutrophils, alteration of plasma thrombin–antithrombin complex and fibrinogen levels *(182)*. However, the investigators could not conclude whether the observed effects were size- or chemical-specific. Similarly, rats exposed to ultrafine carbon particles showed increased heart rate and reduced heart rate variability, but no indication of an inflammatory response and no change in the expression of genes having thrombogenic relevance *(183)*.

A potential mechanism for enhanced effects of ultrafine particles may be more effective translocation from the respiratory tract to extrapulmonary sites compared to larger particles. For example, ultrafine elemental carbon particles inhaled by rats were found in brain tissue, and were postulated to reach the brain via translocation along the olfactory nerve following deposition on the olfactory mucosa of the nasopharynx *(184)*. This pathway circumvents the protective

blood–brain barrier of the central nervous system, and provides a direct route for inhaled PM into the nervous system without transport via the systemic circulation. A comparable pathway for translocation of soluble transition metal compounds has also been postulated *(185–187)* but such a pathway may not be limited to ultrafine particles, as soluble manganese particles in the 1–2-μm size range appeared to translocate to the brain, specifically the olfactory bulb, following inhalation exposure *(188)*. Ultrafine particles have also been found to translocate from the respiratory tract to the liver *(189–192)*.

Ultrafine particles may show greater toxicity than larger size modes owing to an enhanced ability to induce cellular damage by differentially affecting cellular organelles *(177)*.

Ideally, attempts to compare effects due to size mode should use PM from the same geographical area. Huang et al. *(193)* exposed human bronchial epithelial cells to extracts of particles collected from ambient air in Taiwan, China, in three size ranges: $PM_{1.0}$ (<1 μm diameter), fine particles and coarse particles. The ability of PM to elicit inflammatory cytokine production and to cause lipid peroxidation was found to depend on particle size, being most evident for the ultrafine particles. The relationship between response and specific chemical components was less definite, suggesting that the observed responses were associated either with different sets of particle components within each size mode or with nonspecific size effects.

In a similar comparative study, using particles collected by ambient concentrators in the Los Angeles area, Li et al. *(177)* examined differences in size and composition of ultrafine, fine and coarse particles in relation to uptake by macrophages and epithelial cells, and their ability to induce oxidative stress. On a per mass basis, the ultrafine particles were more potent than either the fine or coarse modes in this regard. Again, however, it was not clear whether observed effects were due to particle size alone or to chemical characteristics, in that the ultrafine mode would have a higher number concentration and relatively larger surface area per unit mass for potential adsorption than would the larger size modes. More recently, asthmatic and healthy adults exposed to CAPs in which 80% of the mass was coarse and the rest was <2.5 μm showed increases in heart rate and decreases in heart rate variability *(194)*. Thus, in this study coarse PM may have to some extent had an effect on the autonomic nervous system.

In summary, the available evidence provides a still equivocal answer to the question of a nonspecific role for PM in modulating toxicity and the extent to which size determines toxicity. As noted, the determination of toxicity by physical size cannot be readily separated from correlates of size, such as chemical composition, number concentration or surface area. Even solubility may play a role in this regard, and solubility is another physical factor that differs between different particle size modes *(195)*. Characterizing the role of surface area is complex for PM because much of the mass is soluble salts, but for insoluble particles

composed of low-toxicity material, the surface drives inflammatory responses *(196)*. Furthermore, the specific bioactivity of ambient PM may actually depend on the relative proportion of soluble vs insoluble mass in the exposure atmosphere *(197)*. For example, when PM was collected from various sites and tested for adjuvant activity, the water-insoluble fraction was generally more potent than the water-soluble fraction *(198)*. Thus, in several respects, potential independent consequences of size and particle chemistry in determining toxicity cannot readily be separated

Chemical composition as a modulator of PM toxicity

There is ample evidence to suggest that specific chemical properties of PM link with biological responses *(108)*. As noted, various specific chemical components of ambient PM have been targeted for study to support the plausibility of findings of epidemiological studies and to support the development of hypotheses for testing in observational studies. The following sections discuss evidence for toxicity of these chemical constituents, independent of other potential modulating factors.

Elemental and organic carbon

A large fraction of ambient PM in many areas is derived from combustion processes and, therefore, contains significant amounts of carbon, both as elemental and as organic carbon. Either elemental or organic carbon, or both, may contribute to the toxicity of PM. For example, both the elemental and organic carbon components of CAPs were associated with changes in brachial artery diameter in young healthy adults *(123,199)*. An association between elevated indices of oxidative stress in plasma and carbon black, which generally consists of a mixture of partially combusted hydrocarbons, has been noted *(200)*, as was an association between exposure to carbon black and altered heart rate variability *(201)*. Lipid peroxidation in human bronchial epithelial cells was found to be correlated with both the elemental and organic carbon contents of CAPs collected in Taiwan, China *(193)*.

Although organic carbon can comprise a substantial portion of the mass of ambient PM in most locations, there has been little examination of effects from specific organic carbon components on health outcomes related to PM. One key exception is diesel exhaust particles (DEP). Studies with DEP, as well as some other organic carbon sources, has provided insight into groups of organic carbon components and their potential toxicity.

Li et al. *(176)*, using an in vitro assay, showed that DEP and concentrated PM_{10} and $PM_{2.5}$ induced oxidative stress in alveolar macrophages, a response found with the particulate-associated organic fraction and, especially, for particles highest in PAH. Organic chemicals adsorbed on the surface of some ultrafine particles have been shown to mimic the effects of intact particles in assays

assessing mitochondrial damage and production of reactive oxygen species (ROS) *(202,203)*. Such effects can also be reproduced by functionalized aromatic and polar chemical groups fractionated from DEP *(204,205)*. These compounds are relevant, because the aromatic fraction is enriched in PAHs whereas the polar fraction contains several oxy-PAH compounds, including quinones *(204,205)*. Quinones are able to use the redox cycle and produce ROS, whereas PAHs can be converted to quinones by cytochrome P-450, epoxide hydrolase and dihydrodiol dehydrogenase *(206)*; thus, quinones may be involved in PM-induced oxidative stress *(206,207)*. In contrast, the aromatic chemical fraction induced an effect also seen with a mixture of PAHs. Ambient ultrafine PM induced a combination of polar and aromatic species effects, whereas polystyrene ultrafine particles were inactive in this regard. Furthermore, the aliphatic fraction did not affect ROS production. The PAH component of urban PM has also been implicated in PM-related mutagenicity *(208)*, and prenatal exposure to PAHs resulted in chromosomal aberrations in umbilical cord blood *(209)*. These experiments suggest that the effects of DEP and possibly other types of particle are mediated by chemicals that may be adsorbed on to the particles' surfaces rather than being due to the particle core, and that these adsorbed chemicals probably include organic carbon compounds.

Transition metals and metal compounds

A role for transition metallic species in producing adverse health effects is based on their potential for oxidative activity, resulting in the production of reactive oxygen species. Similar to the quinones, soluble forms of these metals can be involved in reactions involving electron transfer and redox cycling that produce free radicals.

Elevated oxidative stress in the lungs and hearts of rats exposed to CAPs in Boston and residual oil fly ash was most strongly associated with the metal fractions of these particles *(151)*. Molinelli et al. *(210)* exposed a human airway epithelial cell line to aqueous extracts of PM collected in the Utah Valley, the site of a steel mill. Part of the extract was treated to remove cations, including transition metals. Cells exposed to the untreated extract showed a concentration-dependent increase in the inflammatory mediator IL-8 compared to controls, whereas cells incubated with the treated extract showed no change in IL-8. This suggests that the removal of metal cations attenuated cellular responses to the aqueous extract, and supports a role for transition metal involvement in this aspect of PM toxicity. In this regard, cultured human T cells exposed to 1-μm carbon particles or particles containing both carbon and iron showed increased production of ROS with the latter but not with the former *(211)*.

It is unclear whether all PM-associated transition metals are relatively equitoxic or whether a relative ranking of toxicity related to specific metal content of ambient PM can be made. Relative water solubility may also be a factor in

modulating biological response. Using aqueous extracts of filter-collected PM_{10} obtained from Utah Valley before, during and after closure of a local steel mill, Frampton et al. *(212)* avoided the issue of water solubility vs insolubility as a modulating factor in examining effects of these extracts on human respiratory epithelial cells in vitro in terms of oxidant capacity, cytotoxicity and induction of pro-inflammatory cytokine expression. The extract with the lowest metal content, specifically soluble iron, copper and zinc, showed no cytotoxicity, minimal induction of cytokines and lowest oxidant generation ability compared to extracts from filters having higher metal content. However, when metals were removed from the extract prior to exposure there was still an effect of the extracts on at least one endpoint, namely phagocytic activity of macrophages. Thus, the soluble metals were probably not the only component responsible for the observed effects.

There is additional evidence for effects of soluble metals that may relate to health outcomes associated with PM exposure. When ambient PM samples from St Louis, Washington, DC, Düsseldorf and Ottawa were tested for toxicity, the observed greater response to the PM from Ottawa was postulated to be due to its higher content of water-soluble metals *(213)*. Other studies have indicated that zinc in PM may be responsible for various pulmonary effects, such as inflammation, necrosis and airway hyperreactivity *(214–217)*. Human bronchial epithelial cells exposed to PM extracts collected in Taiwan, China showed a correlation between cytokine production and metal content, with effects on some cytokines correlating with chromium and manganese and others with iron and chromium *(194)*. In a study using residual oil fly ash, particles with higher zinc content resulted in greater pulmonary inflammation and airway responsiveness than did particles with higher nickel or vanadium content *(217)*. In a similar study, human bronchial epithelial cells were exposed to concentrated fine fraction PM *(132)*. The greatest correlation to the biomarker of response, namely NF-κB (an indicator of cellular stress), was seen with residual oil sources, using nickel and vanadium as markers. Mice with induced allergic airway disease were found to have increased pro-inflammatory cytokines following exposure to $PM_{2.5}$ recovered from ambient air filters from different areas, but only PM having a higher metal content (specifically zinc, magnesium, lead, copper, cadmium and arsenic) resulted in increased airway responsiveness *(218)*. These apparent differences in responses to various particles in differing model systems suggest that the endpoint examined is critical in deriving conclusions as to the toxicity of specific metals, and also that effects may be linked to the specific valence state of metals.

Secondary inorganic sulfates and nitrates

Schlesinger & Cassee *(219)* provided an extensive review of the toxicology of secondary inorganic aerosols, namely sulfates and nitrates (including acidic species), in relation to health outcomes considered in epidemiological studies on

exposures to ambient PM. The toxicologically significant secondary inorganic particles were probably those having strong acidity, namely sulfuric acid, ammonium bisulfate and, under some unusual atmospheric conditions, nitric acid. Some of these same PM characteristics have been associated with adverse health effects in epidemiological studies. Nonetheless, Schlesinger & Cassee *(219)* concluded that the toxicological evidence did not support a role for secondary inorganic aerosols in adverse health outcomes noted in the epidemiological studies. They reached this conclusion because the ambient concentrations of particulate sulfate are generally much lower than those associated with apparent health effects in the controlled studies. Furthermore, the physicochemical characteristics of the sulfate used in the laboratory studies may have differed from the characteristics of the particles to which human populations are actually exposed in ambient air. Of course, this same limitation probably holds for other PM surrogates used in controlled exposure studies. Other studies also indicate that sulfate may not be of significant toxicological importance in terms of overall effects of PM exposure. In a study using CAPs, effects on a biomarker of cellular stress in human bronchial epithelial cells exposed to concentrated fine PM were not correlated with ambient sulfate, even though sulfate constituted 65% of the particulate mass *(132)*. Effects were, however, clearly correlated with certain metals, such as vanadium and nickel from the PM associated with residual oil combustion. Similarly, in the study of Huang et al. *(193)*, metals were associated with release of cytokine whereas sulfate was not.

Furthermore, toxicological effects associated with primary metal sulfates should not be attributed to a generic species ("sulfates"), as secondary sulfate compounds, thought to be primarily ammonium salts, have negligible health effects *(220)*.

Crustal-associated chemicals

Early studies often used ash from the Mount St Helens volcanic eruption as a surrogate for crustal material. One advantage of using this material is that it isolates the inorganic metal oxides from humic and other organic material associated with soil dust normally found in PM. The studies using volcanic ash tended to show that such particles were relatively inert and generally non-inflammatory *(221)*.

Some recent studies have examined effects of other components generally associated with crustal PM. Using fine particulate mode CAPs from the Boston area, Clarke et al. *(222)* noted that aluminium and silicon were correlated with increased pulmonary neutrophils in lung lavage samples and increased total peripheral blood white cell counts in dogs. However, since crustal PM does not comprise a large fraction of material in the fine particulate mode, the investigators hypothesized that the findings indicated that the aluminium–silicon factor was a surrogate for other particles. Batalha et al. *(223)* showed that exposure

to concentrated ambient $PM_{2.5}$ from Boston resulted in small pulmonary artery constriction in rats that was associated with PM mass, silicon, lead, sulfate, elemental carbon and organic carbon, with silicon having the strongest association. It is unclear as to whether the effect was actually due to the silicon or whether the silicon was a surrogate for another component of PM. Wellenius et al. *(154)* noted that exposure of dogs with coronary occlusion to concentrated $PM_{2.5}$ from Boston resulted in elevation of the ST segment on the ECG, an effect that was not well-correlated with total particle mass or number but was related to silicon mass concentration. In another study using CAPs, Kobzik et al. *(224)* noted that the degree of bronchoconstriction in mice was associated with aluminium–silicon factor. This finding does not necessarily indicate that silicon per se is toxic but that components of ambient PM, with concentrations co-varying with concentration of silicon, may be toxic. Silicon concentrations generally are highly correlated with other crustal elements, such as aluminium and calcium. Finally, Veranth et al. *(225)* observed that some representative soil dusts from the western United States in the fine mode could induce pro-inflammatory cytokine signalling in vitro while other crustal-related PM, namely kaolin clay and aluminium oxide, were benign in this regard.

Biogenically derived PM

PM may have biological sources or may contain specific organic carbon components of biological origin, including pollens, moulds, spores and biological toxins such as bacterial endotoxin. In addition, there is thought to be a major fraction of biogenic-derived organic carbon from atmospheric reactions of volatile organic compounds such as terpenes. Products of biogenic vapour oxidation in the atmosphere include highly oxygenated species, ring compounds and probably organonitrates and amines. The potential health effects of exposure to these biogenically derived chemicals are basically unknown.

Ambient PM of biological origin can have a wide size range, from ultrafine to coarse, thus crossing all size modes of interest for regulatory purposes. While occupational exposure to biological particles has long been known to produce various respiratory tract responses *(226,227)*, the role of biogenic-derived components of ambient PM has not received as extensive study as the other chemical constituents discussed above. Endotoxin levels are generally higher in coarse-mode PM than in smaller size modes, and coarse ambient PM may be more potent than fine PM in inducing pulmonary inflammation if endotoxin is present in the former. Similarly, microbes preferentially found in the coarse fraction of ambient PM may be involved in inflammation induced by these particles *(228)*.

As noted, the coarse mode in particular may contain biologically derived contaminants and such biogenic components may be responsible for the toxicity seen with this size mode *(229,230)*. A number of in vitro studies have shown that coarse-mode particles may induce toxicity. Some of these have indicated

that the coarse mode was more potent than either the fine or ultrafine modes and that potency depended on the season during which particles were collected *(231,232)*, which would probably affect their biogenic constituents. Li et al. *(176)* noted that induction of oxidative stress was correlated with the higher PAH content of coarse PM during the autumn and winter months, while the association with the coarse mode was not observed at other times of the year when the fine-mode PM had higher levels of PAH.

Some PM may act as an adjuvant, i.e. specific PM components may enhance the antigenicity of other inhaled materials, including other types of PM. For example, it has been suggested that DEP may have such adjuvant activity with other antigens *(233,234)*. DEP has been shown to increase the production of IgE in non-atopic individuals *(235)*. While adjuvant activity may only be associated with adsorption of allergens on to PM, such activity may also result from exposures that result in increased tissue sensitivity to subsequent exposure to known allergens *(236)*. When both fine and coarse PM collected from various sites in Europe were tested for adjuvant activity in an allergic mouse model, both size fractions showed various degrees of such activity in combination with allergens *(198)*. Thus, biologically derived PM may be involved in health outcomes in conjunction with other types of PM.

Biopersistence

This property may be important for insoluble particles that could persist and contribute to a PM dose component that accumulates over time. PM contains components with various degrees of solubility. Some components of PM deposited in the lung dissolve in seconds to minutes, and others within hours or days. However, some PM components are sufficiently insoluble to remain in the lung for months or years. Kreyling & Scheuch *(237)* reviewed lung retention and clearance studies using model particles of very low solubility and noted that about one third of insoluble/biopersistent particles are not cleared from the human lungs at all, even under physiological conditions. This conclusion from biokinetics studies is in agreement with the ubiquitously increasing anthracotic pigment; this is well known in human pathology and is caused predominantly by the retention of insoluble and biopersistent black carbon particles, which accumulate with age and blacken the lungs of all individuals, even those living in areas of low PM burden. Based on early studies involving long fibres (>20 μm, e.g. asbestos) showing a considerable inflammatory and carcinogenic potential, new materials such as very long carbon nanotubes may exert an additional toxicological potential according to their biopersistence and extreme aspect ratio *(113)*.

Summary

The toxicological literature documents abundant mechanisms by which PM may adversely affect health *(108,238)*. The National Research Council, in its 2004

report, concluded that substantial progress had been made in this area. Cited work involved the respiratory and cardiovascular systems, as well as immunological and inflammatory responses. As documented in this review as well, inflammation by ROS has emerged as a central and underlying potential mechanism for a variety of adverse effects.

The studies are less informative on the relationship of specific characteristics of PM to adverse health responses. There are difficult methodological challenges in carrying out research to relate particle characteristics to specific health outcomes, arising in part from the many combinations of characteristics and outcomes that might be addressed. Also, results cannot easily be integrated across studies, because investigators have examined PM toxicity using many different protocols, biological endpoints and PM exposure components. Moreover, there is uncertainty arising from the use of surrogates that have still undefined relations to PM in ambient air. Furthermore, the relevance of the findings of laboratory-based studies to the PM exposures of people is uncertain because of the substantial differences in the doses of PM at target sites in the experimental and real-world settings.

The literature is further limited because the experimental models do not address the potential for interactions among PM components or of PM with gases. These interactions might affect dosimetry or directly affect toxicity. Also, many toxicological studies used single materials, with the notable exception of the CAPs studies. However, the relative toxicity of a specific component may depend on its interaction with other components in a specific atmosphere. Particles may act as carriers of chemical compounds that may be toxic and that would not otherwise gain access to the deep regions of the respiratory tract, as in the example of semi-volatile compounds. Particles may also act as catalysts for chemical reactions on their surfaces *(191)*. In terms of particle–particle interactions, while concentrations of organic and elemental carbon in a study with CAPs were associated with changes in brachial artery diameter in humans *(123,199)*, and sulfate alone was not associated with any changes, there was evidence that organic carbon and sulfate may have interacted in producing the effects. In another example of potential particle–particle interaction, Pinkerton et al. *(239)* postulated that the effect of ultrafine combustion particles on reduction of cell proliferation in regions beyond the terminal bronchiole in neonatal rats was due to interaction between soot and iron in the particles, making the latter chemical more bioavailable and, thus, allowing participation in the Fenton reaction and leading to the production of ROS. In a final example, transition metals have been proposed to interact with organic carbon PM components in the generation of ROS *(240)*.

Different PM components may target different biological systems. Thus, the combination of the biological endpoint examined along with the chemical component assessed may determine whether toxicity is observed. For example,

Osornio-Vargas et al. *(241)* exposed murine cells to PM_{10} and $PM_{2.5}$ recovered from filters sampling air in Mexico City to compare cytotoxic and proinflammatory effects of these two size fractions. The PM induced different biological effects depending on the specific sampling site and particle size.

In spite of these limitations, the toxicological evidence is clear in linking adverse biological responses to PM exposure. Toxicological studies have shown that the ultrafine, fine and coarse size modes may result in biological responses that could plausibly contribute to the health outcomes observed in epidemiological studies. The findings of epidemiological studies of acute and chronic health effects suggest that $PM_{2.5}$, which includes PM in the ultrafine size mode, is associated with a range of adverse health outcomes. However, there are only limited epidemiological data on either ultrafine or coarse PM to complement the toxicological studies of these size fractions.

The toxicological evidence does provide an indication that aspects of PM other than mass alone determine toxicity. In terms of chemical species, the strongest toxicological consistency is with secondary inorganic PM, namely sulfates and nitrates at above-ambient levels, but this consistency is opposed by a lack of effect in controlled exposure studies within the ambient concentration range. The findings of the controlled exposure studies contrast with some of the epidemiological findings. There are many potential explanations for this lack of coherence across different lines of investigation and their resolution will require new, interdisciplinary research approaches that better combine toxicology and epidemiology. One such explanation may involve metal sulfates, as noted above.

Controlled exposure studies strongly suggest that transition metals are a chemical component of PM with toxic potential. Experimental studies generally used fairly high exposure concentrations, leaving unclear the relevance of their findings to ambient exposure. Furthermore, the concentration of such metals varies widely geographically, but is generally quite low in ambient air in the United States. A potential role for transition metals at relatively high concentrations in determining risk for health outcomes was demonstrated in parallel toxicological studies and in epidemiological studies of PM associated with steel mill emissions in the Utah Valley. However, recent long-term exposure toxicology suggests that acute biological effects may be due to transition metals at lower ambient concentrations *(132)*.

Experimental studies have indicated that the organic constituents of PM are also likely to be toxicologically active. While the current evidence is not sufficient to develop an unequivocal conclusion as to health hazards from specific organic compounds, the best candidate in this regard is the PAHs or their nitro- and oxy-derivatives. Most studies with biogenic organic carbon-containing aerosols examined bacterial endotoxin, a cell wall component. Endotoxin is present in the coarse mode and may be responsible, at least in part, for the toxicity of this size mode observed in some studies. Parallel epidemiological evidence is still lacking.

Looking across the currently available toxicological evidence, there is little indication that any single physical or chemical property of PM is responsible for the array of adverse health outcomes reported in epidemiological studies. The public health consequences in any particular location may reflect the particular characteristics of PM generated by the mix of local and regional sources. Toxicological studies do, however, indicate that primary PM generated from fossil fuel combustion processes, notably vehicular emissions *(220)*, may be a significant contributor to adverse health outcomes. These emissions generally have a high content of organic carbon and some metals, and may have large PM surface area and number concentration. Regardless of these promising leads, the evidence cannot yet support an indicator for a standard that is more specific than size-fractionated mass alone.

Health effects

The evidence on the health effects of particles comes from several major lines of scientific investigation: characterization of inhaled particles; consideration of the deposition and clearance of particles in the respiratory tract and the doses delivered to the upper and lower airway and the alveoli; animal and cellular studies of toxicity; studies involving inhalation of particles by human volunteers; and epidemiological studies carried out in community settings. The findings of these different lines of investigation are complementary and each has well-identified strengths and limitations. While the findings of epidemiological studies have been given the greatest weight in setting standards for airborne particles, studies on human volunteers (often referred to as "clinical studies") can provide information on exposure–response relationships for acute, transient effects in healthy and potentially susceptible individuals. Studies of this design, involving both healthy persons and adults with chronic diseases, have now been carried out using exposure to concentrated ambient particles.

The epidemiological evidence on PM is now substantial, comprising hundreds of new reports since the previous edition of these guidelines *(1)*. Notably, the range of adverse health effects linked to exposure to ambient particulate pollution has broadened, and now includes not only increased short- and long-term mortality but risk for both adverse respiratory and cardiovascular outcomes (Box 1). The evidence on cardiovascular outcomes has mounted rapidly since 2000 and, as summarized in a 2004 review by a committee of the American Heart Association, there is concern that the association of airborne particles with adverse cardiovascular outcomes is causal *(43)*.

The limitations of the epidemiological studies have been carefully considered since the last review of the evidence in 2000. Issues in interpreting the findings have been those relevant to any body of observational evidence: principally, exposure misclassification and its consequences and the potential for uncontrolled confounding to be producing the associations attributed to PM. Also, particularly

Box 1. Selected health outcomes in epidemiological studies of PM

Mortality	Total Cause-specific
Morbidity	Hospital/admissions Clinic/emergency visits
Cardiovascular	Ischaemic events Arrythmia Cardiovascular events Heart rate variability
Disease status	Symptoms Lung function level Medication use

with regard to the time series and other longitudinal studies, critics have questioned the statistical models used, both with regard to the selection of particular models and to the specification of the variables in the models. Investigators have pursued exposure assessment and methodological research to address these concerns. Finally, a number of key data sets have been re-analysed, including a comprehensive and independent re-analysis of data from two prospective cohort studies, the Harvard Six Cities Study and the American Cancer Society's Cancer Prevention Study II (CPS II) *(242)*. Re-analyses of data from major time series studies were also completed and reported in 2003; the re-analyses were carried out because of the identification of the potential for bias from the default settings in widely used statistical software *(243)*.

One critical uncertainty in interpreting the epidemiological studies was based on limited evidence on the contribution of particles in outdoor air to total personal (and population) exposure. Because most time is spent indoors, ambient particles would make a substantial contribution to personal exposure only if they penetrated into the indoor spaces where time is spent. Exposure studies carried out in the United States and Europe showed that particles in outdoor air contributed substantially to personal exposures and to temporal variation in personal exposures *(108)*. These findings provided support for using central site measurements of ambient particle concentrations as a surrogate for changes in personal exposures in epidemiological studies.

Exposure misclassification may bias risk estimates upward if the pattern of measurement error is differential with risk for the occurrence of the outcome; for example, in a case–control study relying on an exposure questionnaire, exposures to air pollution might be reported with an upward bias by cases compared with unaffected controls. However, such upward bias is unlikely to affect the findings of the most widely used epidemiological designs. Random misclassification is a pervasive concern; in general, this type of misclassification tends to reduce estimates of effect towards the null, i.e. finding no effect. A detailed analysis for daily time series studies led to the conclusion that measurement error would lead to an underestimation of effect under most conditions *(244)*. When air pollution

measurements are available for only one day out of six, as is generally the case in Canada and the United States, use of such data may also result in underestimation of the effects of short-term exposure if an exposure on a particular day has an effect over several days *(245)*.

For the daily time series studies, a specific problem in the application of widely used statistical software was identified in 2002. Many of the time series data sets had been analysed with generalized additive models, using Splus software. The default convergence criteria were not sufficiently stringent for the estimation of risk coefficients in the daily time series data. While the resulting bias had complex origins and its magnitude varied from study to study, there was a general consequence of having upwardly biased estimates of risk from the daily time series analyses. At about the same time, careful examination of the routine for calculating standard error in the Splus *gam* function identified an approximately 10% underestimation. These methodological problems led USEPA to call for re-analyses of key data sets using alternative approaches. The resulting report on the re-analyses was published in 2003 *(243)*. Confounding is always of concern in interpreting the findings of observational studies. Confounding arises when the effect of a factor other than that being studied biases the effect of the factor under study; for confounding to occur, the potential confounding factor needs to be both associated with the outcome of interest and the factor under investigation *(246)*. In carrying out studies, epidemiologists use both design and analytical strategies to control for any bias from confounding.

In studies of air pollution and health, confounding has been raised as a concern with regard to mortality studies, both the daily time series studies and the longer-term cohort studies. In the daily time series studies, temperature and other aspects of weather have been the principal potential confounding factors; temperature and humidity, along with season, have been controlled in the daily time series studies with approaches that involve inclusion of temperature (and relative humidity) variables in the models and the use of temporal smoothing methods that account for the well-known seasonality of mortality (the highest rates occurring across the coldest months and the lowest rates across the warmest months).

The potential for confounding to have biased the findings of the daily time series studies has been explored in a number of ways. Because temporal confounders, such as temperature and influenza epidemics, are a particular concern, models have been used that incorporate these factors and also temporally smooth their effects. The sensitivity of findings to the degree of smoothing provides one indication of potential confounding. Various models have also been used to assess the extent to which control of confounding is model-dependent *(247)*.

Concern for confounding also extends to the long-term cohort studies. Confounding would affect the results of these studies if aspects of lifestyle or environmental exposures other than air pollution were also linked to city of residence of the study participants, the link to air pollution exposure in the cohort studies.

Potential confounding was considered in the original analyses of the cohort studies and given additional consideration for the Harvard Six Cities Study and CPS II in the re-analysis *(248)*. The list of confounders considered was extended and some were incorporated as time-dependent variables.

Since the previous review *(1)*, a number of reports have examined the consequences of rapid changes in ambient pollution, including PM, associated with changes in regulation or sources. These "quasi-experimental" approaches have the potential to be informative because the biologically arbitrary timing of the intervention ensures that the change in exposure is not linked with levels of potential confounding factors. The follow-up of consequences of such changes in exposure has been referred to as "accountability" research; the Health Effects Institute has published a monograph that elaborates this concept and the potential for accountability research to provide new insights into the health effects of air pollution *(247)*.

Several recent reports illustrate the approach. Clancy et al. *(249)* tracked mortality in Dublin and the remainder of Ireland before and after the implementation of a ban on coal burning in Dublin. Mortality from cardiovascular disease dropped more sharply in Dublin than in the remainder of the country after the ban. In China (Hong Kong Special Administrative Region), Hedley and colleagues *(250)* assessed the impact of a mandated reduction in the sulfur content of fuels. Heinrich et al. also documented the decline in chronic respiratory symptoms that followed improvements in air quality in Germany following unification *(251)*. The findings of this line of research can provide evidence reinforcing the causality of associations.

Table 2. Review of studies with concentrated PM

Article title	Study design	Population	Exposure
Comparing inhaled ultrafine versus fine zinc oxide particles in healthy adults: a human inhalation study.	Clinical trial	12 healthy adults	Inhalation of 500 μg/m^3 ultrafine (<0.1 μm diameter) zinc oxide, the same mass of fine zinc oxide, and filtered air while at rest for 2 hours
Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults.	Randomized crossover trial	25 healthy adults	2-hour inhalation of approximately 150 μg/m^3 fine CAPs plus ozone (120 ppb) vs response to the inhalation of filtered air
Exposure to concentrated ambient air particles alters hematological indices in humans.	Clinical trial	20 young adults	Mean PM mass of 120.5 +/– 14.0 μg/m^3 for 24 hours (n = 15) or filtered air (n = 5)

Human exposure studies

Since the 2000 review *(1)*, several groups have exposed volunteers to PM, using a particle concentrator to bring ambient PM to a concentration at which transient, acute effects are expected to occur. The mixture to which the volunteers are exposed has been referred to as concentrated ambient particles or CAPs. Studies using CAPs have the strength of exposing volunteers to "real-world" ambient PM rather than a surrogate. There are several potential limitations, including the possibility that the concentration alters the PM characteristics and the generalizability of findings from one particular location and time to PM exposures more generally. Additionally, there is inherent day-to-day variability of exposure as the ambient PM mixture changes.

Nonetheless, there is a growing number of reports of findings of studies with CAPs (Table 2). The studies have included both healthy volunteers and persons with asthma or COPD. These controlled studies are time-consuming and laborious and consequently population sizes are small, leading to concern for adequate power. Additionally, exposures have been carefully designed to avoid the risk of serious consequences. In the studies, a variety of physiological outcomes and biomarkers has been considered and the studies are most useful for the mechanistic insights they provide, rather than for identifying thresholds below which effects do not occur.

Across the studies, a range of outcomes has been considered (Table 2), with findings showing that some outcomes were affected by exposure to CAPs. The results are not fully consistent, for example, in showing evidence for inflammation, and some studies provide null findings.

Findings	Reference
No differences were detected between any of the three exposure conditions at this level of exposure.	Beckett et al. *(252)*
CAPs plus ozone caused a significant brachial artery vasoconstriction compared with filtered air inhalation (–0.09 +/– 0.15 mm vs +0.01 +/– 0.18 mm, $P = 0.03$). No significant differences in flow-mediated dilatation (+0.29 +/– 4.11% vs –0.03 +/– 6.63%, $P = 0.88$), nitroglycerin-mediated dilatation (+3.87 +/– 5.43% vs +3.46 +/– 7.92%, $P = 0.83$), or blood pressure responses between exposures.	Brook et al. *(123)*
Exposure of healthy volunteers to CAPs was associated with decreases in both white blood cell count and lactate dehydrogenase and increased concentrations of fibrinogen in the blood.	Ghio et al. *(253)*

▶

Article title	Study design	Population	Exposure
▶ Controlled exposures of healthy and asthmatic volunteers to concentrated ambient particles in metropolitan Los Angeles.	Clinical trial	12 healthy and 12 asthmatic adults	Once to 2 hours of 200 μg/m^3 CAPs in the fine (<2.5 μm) size range and once to filtered air
Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers.	Clinical trial	38	Particle concentrations from 23.1 to 311.1 μg/m^3 for 2 hours
Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability.	Clinical trial	10 elderly subjects, 22 young subjects	Particle concentrations 6–10 times normal Chapel Hill air of $PM_{2.5}$
Altered heart-rate variability in asthmatic and healthy volunteers exposed to concentrated ambient coarse particles.	Clinical trial	12 mildly asthmatic and 4 healthy adults	Filtered air followed by concentrated coarse particles (mean 157 μg/m^3 for 2 hours)
Exposures of elderly volunteers with and without chronic obstructive pulmonary disease (COPD) to concentrated ambient fine particulate pollution.	Clinical trial	13 elderly volunteers with COPD and 6 age-matched healthy adults	200 μg/m^3 CAPs <2.5 μm in diameter and filtered air for 2 hours
Respiratory responses to exposures with fine particulates and nitrogen dioxide in the elderly with and without COPD.	Clinical trial	6 healthy subjects and 18 volunteers with COPD	(*a*) filtered air; (*b*) 0.4 ppm nitrogen dioxide; (*c*) CAPs ($PM_{2.5}$) at 200 μg/m^3; and (*d*) CAPs and nitrogen dioxide together for 2 hours

Findings	Reference
Neither healthy nor asthmatic subjects showed significant changes in symptoms, spirometry or routine haematological measurements attributable to CAPs exposure compared with filtered air. Both groups showed CAPs-related (*a*) decreases of columnar cells in induced sputum after exposure, (*b*) increases in certain blood mediators of inflammation (i.e. CAM-1 and IL-6) and (*c*) parasympathetic stimulation of heart rate variability. In the asthmatic group, systolic blood pressure modestly increased during filtered air exposure and decreased during CAPs exposure, whereas the pattern was reversed in the healthy group.	Gong, Sioutas & Linn *(254)*
Mild increase in neutrophils in both the bronchial and alveolar fractions in individuals exposed to CAPs (8.44 +/– 1.99 and 4.20 +/– 1.69%, respectively, in those with the greatest exposure) relative to filtered air (2.69 +/– 0.55 and 0.75 +/– 0.28%, respectively). Blood obtained 18 hours after exposure to CAPS contained significantly more fibrinogen than samples obtained before exposure.	Ghio, Kim & Devlin *(255)*
Elderly people experienced significant decreases in both time and frequency of heart rate variability immediately following exposure. No CAPs-induced changes in heart rate variability were found in young volunteers exposed to CAPs in a previous study.	Devlin et al. *(256)*
Relative to filtered air, exposure to concentrated coarse particles did not significantly alter respiratory symptoms, spirometry, arterial oxygen saturation or airway inflammation, according to exhaled nitric oxide and total and differential cell counts of induced sputum. Electrocardiograms showed small (P <0.05) increases in heart rate and decreases in heart rate variability, which were larger in healthy than in asthmatic subjects. Cardiac ectopy did not increase.	Gong et al. *(194)*
A significant negative effect of CAPs on arterial oxygenation was more pronounced in healthy subjects. Peripheral blood basophils increased after CAPs in healthy people but not in COPD patients. In both groups, red cell counts increased slightly 1 day after exposure to filtered air but not to CAPs. Pre-exposure ectopic heartbeats were infrequent in healthy subjects but increased modestly during/after CAPs exposure relative to filtered air. Ectopic beats were more frequent in COPD patients, but decreased modestly during/after CAPs relative to filtered air. Heart rate variability over periods of several hours was lower after CAPs than after filtered air in healthy elderly subjects but not in COPD patients. Unexpectedly, individuals with COPD appeared less susceptible than healthy elderly individuals.	Gong et al. *(257)*
Most respiratory responses showed no statistically significant responses attributable to separate or combined effects of CAPs and nitrogen dioxide. Maximal mid-expiratory flow and arterial oxygen saturation (measured by pulse oximetry) showed small but statistically significant decrements associated with CAPs, greater in healthy than COPD subjects. CAPs exposure was also associated with lower percentages of columnar epithelial cells in the sputum.	Gong et al. *(258)*

▶

Article title	Study design	Population	Exposure
▶ Inhalation of $PM_{2.5}$ does not modulate host defense or immune parameters in blood or lung of normal human subjects.	Clinical trial	38	CAPs between 0.1 and 2.5 µm in diameter in concentrations ranging from 23.1 to 311.1 µg/m^3
Health effects of acute exposure to air pollution. Part II: Healthy subjects exposed to concentrated ambient particles	Clinical trial	38 (CAPs n = 30, filtered air n = 8)	In the CAPs-exposed group, the concentration of $PM_{2.5}$ varied from 23.1 to 311.1 µg/m^3; for the filtered air group, mean particle concentration was 2.9 µg/m^3
Human pulmonary responses to experimental inhalation of high concentration fine and ultrafine magnesium oxide particles.	Clinical trial: before and after where subjects served as their own controls	6	Mean +/– standard deviation cumulative magnesium dose was 4138 +/– 2163 min x mg/m^3. By weight, 28% of fume particles were ultrafine (<0.1 µm in diameter) and over 98% of fume particles were fine (<2.5 µm in diameter)
Effects of inhaled iron oxide particles on alveolar epithelial permeability in normal subjects.	Clinical trial: subjects served as their own controls	16	Iron oxide particles (1.5 µm) having either high or low water-soluble iron content (3.26 +/– 0.25 (SE) and 0.14 +/– 0.04 µg soluble iron per mg particles, respectively) for 30 min at an average mass concentration of 12.7 mg/m^3
Pulmonary function, diffusing capacity, and inflammation in healthy and asthmatic subjects exposed to ultrafine particles.	Series of 4 randomized, double-blind controlled crossover trials	Study 1: 12 Study 2: 12 Study 3: 16 Study 4: 16 Total: 56	Healthy subjects were exposed to carbon particle concentrations of 10, 25 and 50 µg/m^3, while asthmatics were exposed to 10 µg/m^3
Acute blood pressure responses in healthy adults during controlled air pollution exposures.	Clinical trial	23 normotensive, non-smoking, healthy adults	Mean concentrations of $PM_{2.5}$ were 147 +/– 27 vs 2 +/– 2 µg/m^3 and those of ozone were 121 +/– 3 vs 8 +/– 5 ppb

Findings	Reference
Mild increase in neutrophils in both the bronchial and alveolar fractions in subjects exposed to the highest concentration of CAPs compared to neutrophils in the fluids of those exposed to filtered air. No change in the percentage of lymphocytes or alveolar macrophages recovered in the lavage after inhalation of the highest particle levels, or in the proportion of lymphocytes in the bronchoalveolar lavage fluid expressing CD3, CD4, CD8, CD19 or activation markers CD25 or CD69. Particle inhalation did not affect the expression of CD11b, CD64, CD16, CD14, CD71 on alveolar macrophages, nor was there an effect on phagocytosis or oxidant generation following stimulation with zymosan A. IL-6 and IL-8 levels detected by enzyme-linked immunosorbent assay in the bronchoalveolar lavage fluid were unrelated to inhaled particle levels. The distribution of lymphocyte subsets in blood obtained 18 hours after exposure to CAPs did not differ from that found before exposure. Ambient air particles are capable of inducing a mild inflammation in the lower respiratory tract but have no effect on immune phenotype or macrophage function under the conditions tested.	Harder et al. *(259)*
CAPs induced a modest degree of airway inflammation as judged by lavage, but this effect was not reflected in biopsy tissues from proximal airways.	Holgate et al. *(260)*
No significant differences in bronchoalveolar lavage inflammatory cell concentrations, bronchoalveolar lavage IL-1, IL-6, IL-8, tumour necrosis factor, pulmonary function or peripheral blood neutrophil concentrations post-exposure compared with control.	Kuschner et al. *(261)*
Inhalation of iron oxide particles did not cause an appreciable alteration of alveolar epithelial permeability, lung diffusing capacity, or pulmonary function in healthy subjects under the studied conditions.	Lay et al. *(262)*
Exposing 16 normal subjects to the higher concentration of 50 µg/m^3 caused a reduction in maximal mid-expiratory flow rate and carbon monoxide diffusing capacity at 21 hours after exposure. There were no consistent differences in symptoms, induced sputum or exhaled nitric oxide in any of these studies.	Pietropaoli et al. *(263)*
Significant increase in diastolic blood pressure at 2 hours of CAPs + ozone above the 0-hour value. This increase was significantly different from a small 2-hour change with particle-free air. Further investigation of the CAPs + ozone response showed a strong association between the 2-hour change in diastolic blood pressure (and mean arterial pressure) and the concentration of the organic carbon fraction of $PM_{2.5}$, but not with total $PM_{2.5}$ mass.	Urch et al. *(264)*

▶

Article title	Study design	Population	Exposure
▶ The role of soluble components in ambient fine particles-induced changes in human lungs and blood.	Clinical trial	37 young healthy volunteers	Particle concentrations 6–10 times normal Chapel Hill air of $PM_{2.5}$

Mortality

Overview

The effect of PM on mortality has been examined using cross-sectional designs (examining variation in mortality rates across locations having differing PM levels), daily time series designs (examining variation in day-to-day mortality counts in relation to PM concentration, and cohort studies (examining mortality on a long-term basis in relation to an indicator of average exposure to PM). This review does not consider studies that used cross-sectional approaches alone, although such approaches have provided useful insights into the effect of air pollution on health in the past, as, for example, the pioneering analyses of Lave & Seskin *(266–268)*. Some of the time series studies that are based on data from multiple locations also explore variations in exposure across locations as a basis for spatially varying short-term effects of PM.

The evidence from the daily time series studies and the prospective cohort studies is complementary in understanding the extent to which exposure to ambient PM shortens life. Associations observed in the time series studies could reflect only a brief advance in the time of death, perhaps among those already frail because of underlying heart and lung disease. This possibility, referred to as "harvesting" or "mortality displacement", implies that the associations observed in the daily time series studies are not indicating an effect of public health significance. The cohort studies provide information on a longer time frame and their positive findings suggest that the effect of PM on mortality is not a brief displacement of mortality. Analytical approaches to assessing the extent of mortality displacement have also been developed and their results also indicate that any advance of the time of death caused by PM is more than just a few days *(269,270)*.

Daily time series studies of mortality

Since the previous review *(1)*, there has been a substantial expansion in the evidence on PM derived from daily time series studies. There has been a continual flow of publications based on analyses of data from single cities. More importantly, analyses have pooled data from several locations, using a common protocol for analysis of the within-city data and then combining estimates from various locations in order to gain precision and to evaluate the heterogeneity of the effect of PM across the cities. The newer evidence comes from the APHEA 2

Findings	Reference
Sulfate/iron/selenium factor was associated with increased percentage of neutrophils in bronchoalveolar lavage fluid and a copper/zinc/vanadium factor with increased blood fibrinogen. The concentrations of sulfate, iron and selenium correlated highly with PM mass (R >0.75) while the correlations between PM and copper/zinc/vanadium were modest (R = 0.2–0.6).	Huang et al. *(265)*

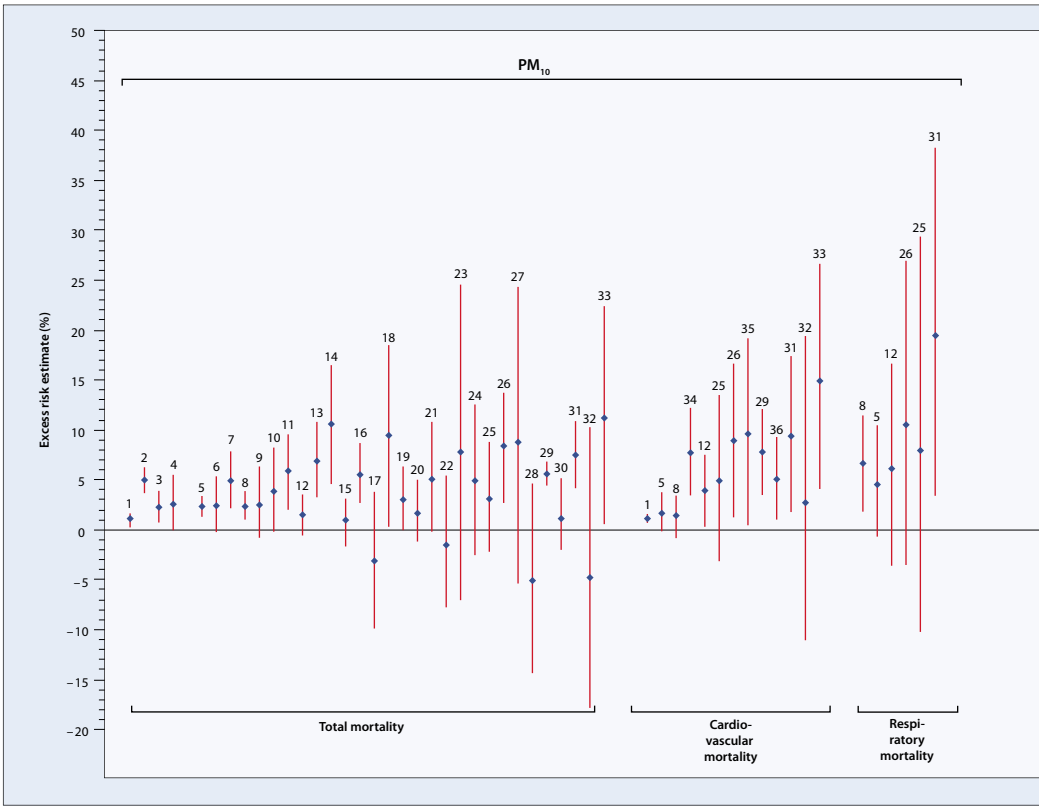
study, NMMAPS in the United States, and from research involving several cities in Canada. These data have been summarized in USEPA's PM criteria document *(3)* and in a meta-analysis carried out by a WHO task group *(2)*. The WHO task group used the updated estimates for those studies with re-analysed data.

In general (Fig. 1 and 2), the evidence from the daily time series studies shows a positive association of PM concentration with risk for total and cause-specific mortality. Fig. 1, taken from USEPA's staff paper *(4)*, summarizes data for North American cities, including analyses of data from various cities in Canada and the United States. The PM indicators include PM_{10}, $PM_{2.5}$ and $PM_{10-2.5.}$ and the analyses considered all-cause and cause-specific mortality. The figure shows generally positive associations of PM with risk across the array of indicators and outcomes, although not all estimates are statistically significant. The data are most limited for $PM_{10-2.5}$, which is often referred to as the "coarse mode."

The WHO task group focused on European studies and its analyses thus complement those of USEPA. Table 3 provides the pooled estimates for various PM indicators and Fig. 2 gives the estimates for the individual cities; as with the North American analyses, most estimates were positive. Of the 33 cities, 22 came from the APHEA 2 study. For PM_{10}, the estimate for all-cause mortality was 0.6% (95% CI 0.4–0.8) per 10-$\mu g/m^3$ increase. The revised estimate from the NMMAPS project was 0.21% per 10-$\mu g/m^3$ increase in PM_{10} concentration. There a number of possible explanations for the difference between the European estimate and the NMMAPS estimate, which is based on the 90 largest American cities without any additional selection; these include differences in analytical approach and other aspects of the methodology, as well as the possibility of a difference in the true effect of PM arising from different characteristics or exposure patterns on the two continents. Nevertheless, both bodies of data provide evidence of an adverse effect of PM on short-term mortality at contemporary concentrations. Recent meta-analyses of time series studies conducted outside Europe and the United States have reported comparable summary estimates for daily mortality from all natural causes *(28,29)*.

The effect estimates are larger for cardiovascular and respiratory causes than for all-cause mortality. This pattern is consistent with the hypothesis that persons with underlying chronic heart and lung disease are at greater risk from PM exposure.

Fig. 1. Excess risk estimates for total non-accidental, cardiovascular and respiratory mortality in multi-pollutant (No. 1–4 below) and single-pollutant models for Canadian and United States studies

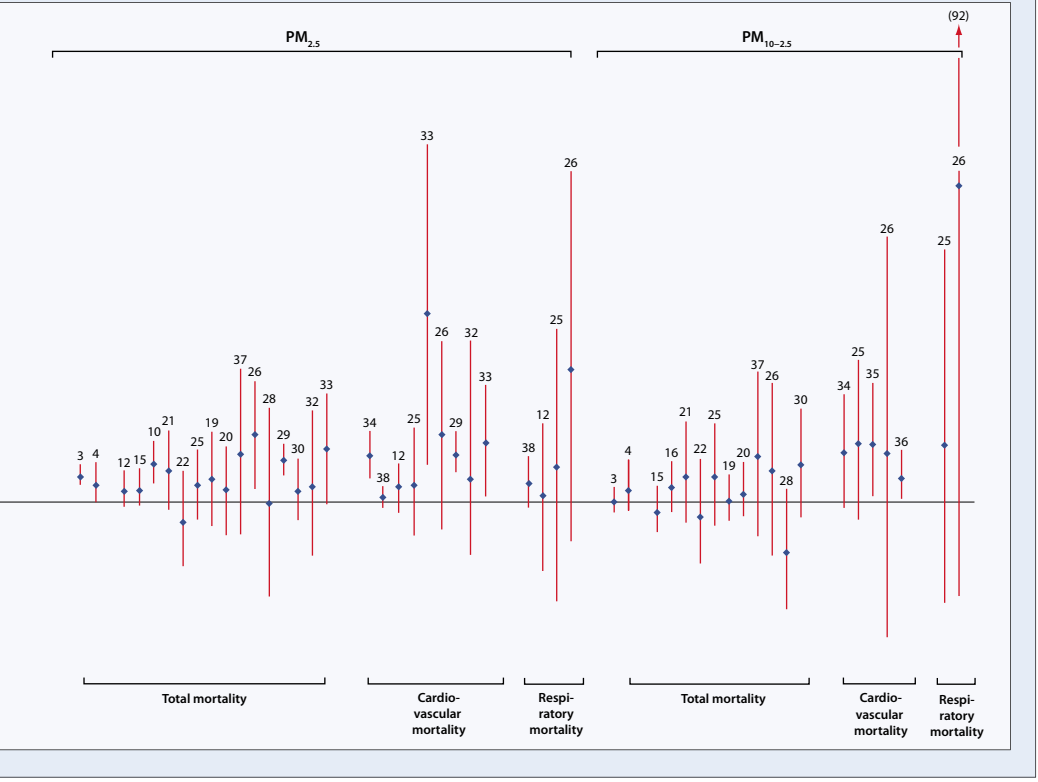


Note. PM increments: 50 μg/m³ for PM_{10} and 25 μg/m³ for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time series studies that did not use a generalized additive model (GAM) or were reanalysed using a generalized linear model (GLM).
Source: US Environmental Protection Agency *(4)*.

Table 3. Summary relative risk estimates (and 95% confidence intervals) for a 10-μg/m³ increase in pollutant for all-cause and cause-specific mortality

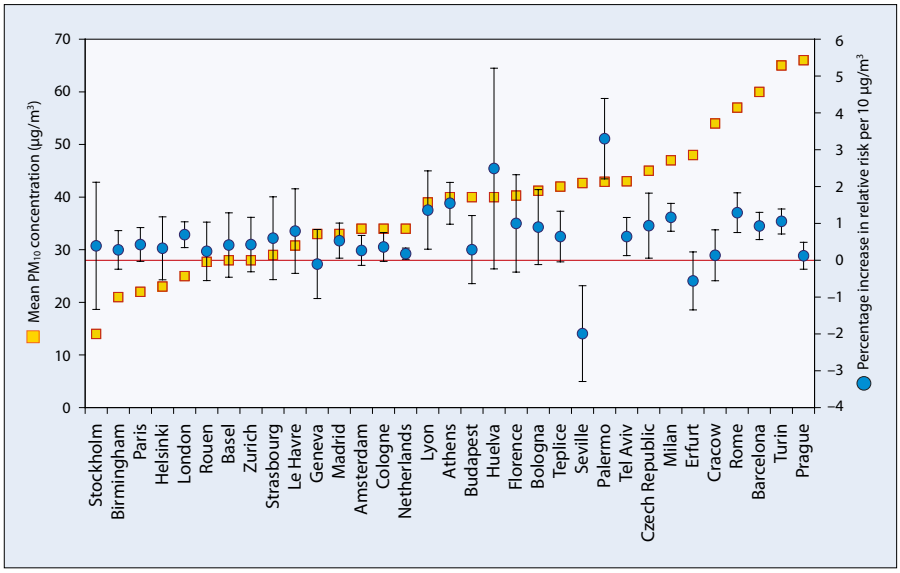
Outcome/disease	Age	PM_{10}	$PM_{2.5}$	Coarse particles	Black smoke	Ozone (8-hour)
All-cause	All ages	1.006 (1.004–1.008) **33** [b]	NA [a] **3**	NA **1**	1.006 (1.004–1.008) **26**	1.003 (1.001–1.004) **15**
Respiratory	All ages	1.013 (1.005–1.020) **18**	NA **1**	NA **1**	1.006 (0.998–1.015) **18**	1.000 (0.996–1.005) **12**
Cardiovascular	All ages	1.009 (1.005–1.013) **17**	NA **1**	NA **2**	1.004 (1.002–1.007) **18**	1.004 (1.003–1.005) **13**

[a] NA = insufficient numbers available for meta-analysis (<4).
[b] Numbers in bold indicate number of European studies available.
Source: Anderson et al. *(2)*.



1. Dominici et al. *(271)*, 90 United States cities
2. Schwartz *(272)*, 10 United States cities
3. Klemm & Mason *(273)*, 6 United States cities
4. Burnett & Goldberg *(274)*, 8 Canadian cities
5. Moolgavkar *(275)*, Cook County
6. Kinney et al. *(276)*, Los Angeles
7. Schwartz *(272)*, Chicago
8. Ito & Thurston *(277)*, Cook County
9. Schwartz *(272)*, Pittsburgh
10. Styer et al. *(278)*, Cook County
11. Schwartz *(272)*, Detroit
12. Moolgavkar *(275)*, Los Angeles
13. Schwartz *(272)*, Seattle
14. Schwartz *(272)*, Minneapolis
15. Klemm & Mason *(273)*, St Louis
16. Klemm & Mason *(273)*, Boston
17. Schwartz *(272)*, Birmingham
18. Schwartz *(272)*, New Haven
19. Chock et al. *(279)*, Pittsburgh (<75 years)
20. Chock et al. *(279)*, Pittsburgh (75+ years)
21. Klemm & Mason *(273)*, Kingston-Harriman
22. Klemm & Mason *(273)*, Portage
23. Schwartz *(272)*, Canton
24. Schwartz *(272)*, Spokane
25. Ito *(280)*, Detroit
26. Fairley *(281)*, Santa Clara County
27. Schwartz *(272)*, Colorado Springs
28. Klemm & Mason *(273)*, Topeka
29. Tsai et al. *(282)*, Newark
30. Klemm & Mason *(273)*, Steubenville
31. Pope et al. *(283)*, Utah Valley
32. Tsai et al. *(282)*, Elizabeth
33. Tsai et al *(282)*, Camden
34. Lipfert et al. *(284)*, Philadelphia
35. Mar et al. *(285)*, Phoenix
36. Ostro et al. *(286)*, Coachella Valley
37. Klemm & Mason *(287)*, Atlanta
38. Ostro et al. *(288)*, Southern California

Fig. 2. Ranking of PM_{10} effect estimates for all-cause mortality by annual average levels of PM_{10}



Source: Anderson et al. 2004 *(2)*.

Prospective cohort studies of PM and mortality

The effect of PM on mortality in the longer term has been investigated by assessing PM concentration in communities of residence and mortality risk among participants in prospective cohort studies. Long-term studies of PM and mortality cannot be readily carried out, as they require a substantial number of participants, lengthy follow-up, and information on PM exposure and potential confounding factors. Table 4 provides a description of the studies and the key findings.[2] Most of the studies have been carried out in the United States, but findings have been reported for two European studies as well. Full details of the studies have been provided in the original reports and covered in the USEPA criteria document *(3)*. The studies have the common design features of assignment of exposure based on place of residence and having death as the outcome. In all studies, exposures were assigned without individual-level detail, but some studies included information on confounding factors at the individual level. Such designs,

[2] Following the preparation of this chapter considered at the WHO Working Group meeting in October 2005, several additional cohort studies have reported estimates of the effects of long-term exposure to particulate air pollution on mortality from chronic cardiovascular and respiratory disease *(289–291)*. Two studies *(291,292)* report effects of long-term exposure to particulate air pollution that are consistent with those of earlier reports cited in this chapter (RR = 1.11 per 10 µg/m^3 $PM_{2.5}$, 95% CI 0.99–1.25; and 1.16 per 10 µg/m^3 $PM_{2.5}$, 95% CI 1.07–1.26, respectively). Enstrom *(291)* failed to observe increased mortality associated with long-term exposure (RR = 1.01 per 10 µg/m^3 $PM_{2.5}$, 95% CI 0.99–1.03). The discrepancies are discussed by Brunekreef & Hoek *(292)*.

Table 4. Cohort studies of air pollution and mortality

Reference	Population	Follow-up	Findings
Dockery et al. *(293)*	8111 adults in 6 American cities	14–16 years	Mortality rates were most strongly associated with smoking. The adjusted mortality-rate ratio for the most polluted of the cities compared with the least polluted was 1.26 (95% CI 1.08–1.47). Air pollution was positively associated with death from lung cancer and cardiopulmonary disease but not with death from other causes considered together. Mortality was most strongly associated with air pollution with fine particulates, including sulfates.
Pope et al. *(294)*	552 138 adults who resided in one of 151 metropolitan areas when enrolled in a prospective study in 1982 ACS cohort	7 years (1982–1989)	Adjusted relative risks of all-cause mortality for the most polluted areas compared with the least polluted were 1.15 (1.09–1.22) and 1.17 (1.09–1.26) when using sulfate and fine particulate measures, respectively. Particulate air pollution was associated with cardiopulmonary and lung cancer mortality but not with mortality due to other causes.
Pope et al. *(295)*	500 000 adults from ACS cohort	Up to 16 years	Fine particulate and sulfur-oxide-related pollution were associated with all-cause, lung cancer and cardiopulmonary mortality. Each 10-μg/m^3 elevation in fine particulate air pollution was associated with approximately a 4%, 6% and 8% increased risk of all-cause, cardiopulmonary and lung cancer mortality, respectively. Measures of coarse particle fraction and total suspended particles were not consistently associated with mortality.
Abbey et al. *(296)*	6338 non-smoking California Seventh Day Adventists (from AHSMOG cohort)	15 years	For both sexes, PM_{10} showed a strong association with mortality for non-malignant respiratory disease on the death certificate, adjusting for a wide range of potentially confounding factors, including occupational and indoor sources of air pollutants. The adjusted relative risk for this cause of death as associated with an interquartile range difference of 43 days/year when PM_{10} exceeded 100 μg/m^3 was 1.18 (1.02–1.36). In males, PM_{10} showed a strong association with relative risk for lung cancer deaths, relative risk for an interquartile range being 2.38 (1.42–3.97). Ozone showed an even stronger association with lung cancer mortality for males, with a relative risk of 4.19 (1.81–9.69) for the interquartile range difference of 551 hours/year when ozone exceeded 100 parts per billion. Sulfur dioxide showed strong associations with lung cancer mortality for both sexes.

▶

Reference	Population	Follow-up	Findings
▶ McDonnell et al. *(297)*	6338 California Seventh-Day Adventists	15 years	In single-pollutant models, for an interquartile range increase in PM_{10} (29.5 μg/m^3), the relative risks and 95% CI were 1.15 (0.94–1.41) for all causes, 1.48 (0.93–2.34) for underlying or contributory causes and 1.84 (0.59–5.67) for lung cancer mortality. For an interquartile range increase in $PM_{2.5}$ (24.3 μg/m^3), corresponding relative risks (95% CI) were 1.22 (0.95–1.58), 1.64 (0.93–2.90) and 2.23 (0.56–8.94), and for an interquartile range increase in $PM_{2.5-10}$ (9.7 μg/m^3), corresponding relative risks (95% CI) were 1.05 (0.92–1.20), 1.19 (0.88–1.62) and 1.25 (0.63–2.49), respectively. When both $PM_{2.5}$ and $PM_{2.5-10}$ were entered into the same model, the $PM_{2.5}$ estimates remained stable while those of $PM_{2.5-10}$ decreased.
Lipfert et al. *(298)*	National cohort of about 50 000 veterans who were diagnosed as hypertensive in the mid-1970s	21 years	Fine particles indicated no significant (positive) excess mortality risk for this cohort in any of the models considered. Among the positive responses, indications of concurrent mortality risks were seen for nitrogen dioxide and peak ozone, with a similar indication of delayed risks only for nitrogen dioxide. Mean levels of these excess risks were 5–9%. Peak ozone was dominant in two-pollutant models and there was some indication of a threshold in response.
Burnett et al. *(299)*	8 of Canada's largest cities	11 years	Positive and statistically significant associations were observed between daily variations in both gas- and particulate-phase pollution and daily fluctuations in mortality rates. The association between air pollution and mortality could not be explained by temporal variation in either mortality rates or weather factors. Fine particulate mass (<2.5 μm in average aerometric diameter) was a stronger predictor of mortality than coarse mass (2.5–10 μm). Size-fractionated particulate mass explained 28% of the total health effect of the mixture, with the remaining effects accounted for by the gases.
Hoek et al. *(300)*	Random sample of 5000 people from the full cohort of the NLCS study (age 55–69 years) from 1986 to 1994		11% of people with data died during the follow-up period. Cardiopulmonary mortality was associated with living near a major road (relative risk 1.95, 95% CI 1.09–3.52) and, less consistently, with the estimated ambient background concentration (1.34, 0.68–2.64). The relative risk for living near a major road was 1.41 (0.94–2.12) for total deaths. Non-cardiopulmonary, non-lung cancer deaths were unrelated to air pollution (1.03, 0.54–1.96) for living near a major road.

▶

Reference	Population	Follow-up	Findings
▶ Filleul et al. *(301)*	14 284 adults who resided in 24 areas in 7 French cities when enrolled in the PAARC survey in 1974	25 years	Adjusted risk ratios (95% CI) for total suspended particulates, BS, nitrogen dioxide, and nitric oxide for non-accidental mortality were 1.05 (1.02–1.08), 1.07 (1.03–1.10), 1.14 (1.03–1.25) and 1.11 (1.05–1.17) for 10 μg/m^3, respectively.

incorporating exposure at the population level but with individual covariate data, have been termed "semi-ecological". Data from two of the studies, CPS II and the Harvard Six Cities Study, have been independently re-analysed *(248)*.

In general, the studies show a positive association between PM indicators and total and cause-specific mortality, including cardiovascular diseases and lung cancer. In the major studies, the findings are statistically significant and robust to control for confounding, although the possibility of some confounding remains.

Morbidity

Overview

A wide range of morbidity indicators has been investigated in epidemiological studies (Box 1 and Fig. 3); the populations have included infants, children, adults, and various groups considered susceptible to PM. The outcomes include clinical indicators such as hospital admission numbers and counts of visits to emergency departments or clinics, symptom status in persons with underlying chronic heart or lung disease, level of pulmonary function, and various biomarkers. The design approaches include time series studies, "panel studies" or short-term cohort studies of susceptible groups, and cross-sectional studies. Risk for acute events, including myocardial infarction and stroke, has been assessed using the case-crossover design. In this design, the individual is the unit of analysis and exposures are compared in the "case" period during which the event of interest took place and in one or more event-free "control" periods. As for mortality, the literature on morbidity indicators in relation to PM is also substantial. The USEPA criteria document *(3)* provides a summary through to 2004. Selected elements of the evidence are considered in this chapter. This evidence is complementary to the information on mortality, as it covers the full range of adverse health effects from changes in biomarkers to clinical disease. Nevertheless, the recommendations for specific guideline values are largely based on the mortality findings.

Reproductive outcomes

The developing fetus has long been considered at potentially increased risk from exposures during critical periods of development. Maternal smoking is causally associated with a number of adverse effects on reproduction, including increased risk of miscarriage and a reduction of birth weight that averages approximately

250 grams *(316)*. Studies have been carried out using birth certificate data to address maternal exposures to air pollution generally (and PM specifically) and reproductive outcomes; several cohort studies have also addressed reproductive outcomes in relation to air pollution exposure. Although numerous studies have now been carried out, a mixed group of outcomes and pollutants has been studied; some studies have shown associations with indices of maternal exposure to PM *(317,318)*. This emerging area of public health concern needs further research, and the available evidence is not sufficient to be considered in recommending guidelines for PM.

Childhood asthma

Worldwide, asthma is one of the most common chronic diseases of childhood. The underlying increased airways responsiveness that is inherent in asthma may increase susceptibility to inhaled pollutants generally and PM specifically *(319,320)*. The association between exposure to air pollution and asthma has been studied by tracking hospital admission and clinic visit rates and by panel studies of children that evaluate symptom status, medication use, or physiological indicators in relation to PM exposure. Delfino et al. *(321)* reported findings of a representative study of 19 California children who were tracked for two-week intervals with measurement of FEV_1; personal exposures to PM were monitored as well. In Europe, the multicentre PEACE study addressed childhood asthma and air pollution, including PM *(322)*. While not all studies have linked PM to increased risk of exacerbation, the weight of evidence indicates that ambient PM does adversely affect children with asthma.

Hospital admissions

Extensive time series analyses have addressed PM and the risk of hospital admission and of visiting an emergency department. These are both outcome measures that indicate a level of acuteness requiring immediate medical care. The USEPA staff paper *(4)* provides a summary of effect estimates from American and Canadian studies (Fig. 3). There is consistent evidence for increased risk for cardiovascular and respiratory outcomes, for both hospital and emergency department admissions.

Cardiovascular outcomes

The body of evidence on exposure to PM and cardiac outcome measures has grown rapidly over the last decade *(3,43)*. The range of outcomes considered extends from subtle indicators of physiological abnormality to myocardial infarction and sudden death *(43)*. As reviewed above, there is evidence of clinically relevant morbidity manifest in increased hospital admission rates for cardiovascular disease in association with higher levels of PM. The observational research is complemented by experimental studies that address underlying pathogenetic

mechanisms for these effects. One key issue in interpreting the evidence for cardiovascular effects has been the mechanisms by which inhaled particles could have cardiac effects. Possibilities include secondary effects of cytokines released in the lungs or neural responses to inhaled particles, effects on autonomic control of cardiac function, and primary effects from particles that move across the epithelial barrier of the lungs to reach the systemic circulation *(43)*.

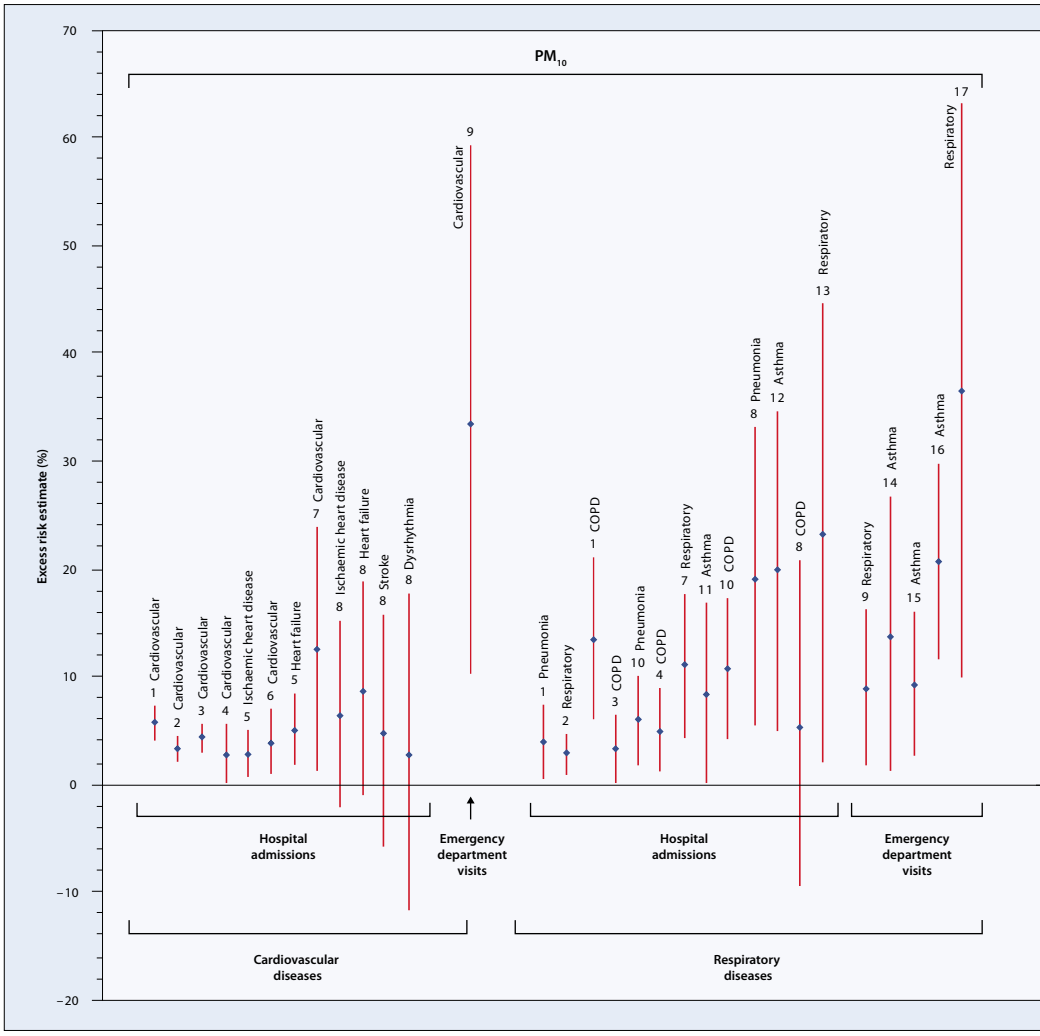
Ultrafine particles

To date, research on specific particle fractions (whether defined by physical or chemical characteristics) and health has been relatively limited. There is sufficient literature on ultrafine particles, however, to warrant a specific review. The extent of ultrafine particle pollution has been indexed for research by the particle number concentration of particles >0.1 μm in aerodynamic diameter. Particles in this size range are typically generated by combustion processes or formed from gaseous pollutants by photo-oxidation. Depending on size, the half-life can be very short, but under typical urban conditions the half-life is around one hour for 20-nm particles *(42)*. Available monitoring data from selected locations show that $PM_{2.5}$ mass concentration and ultrafine particle number concentrations are only moderately correlated over time *(40,323)*. However, high concentrations of ultrafine particles are recorded immediately adjacent to busy roads, with concentrations decreasingly rapidly at increasing distance from roadways *(73)*. There is higher spatial variability for ultrafine particles than for fine particles in urban areas.

To date, there have been only a limited number of studies on the association of measures of ultrafine particles with risk of adverse health effects. Wichmann et al. evaluated the attribution of PM effects to specific size fractions, including both the number concentration and the mass concentration of particles in three size classes of ultrafine (0.01–0.1 μm) and three size classes of larger fine particles (0.1–2.5 μm) *(324)*. Total, cardiovascular and respiratory mortality counts were analysed as health outcomes, using best single-day lag and best polynomial distributed lag models for the air pollution measures for lags of 0–5 days. In all size classes, mass concentration and number concentration were associated with total mortality. Mass concentration of fine particles showed the strongest effect on respiratory deaths with a lag of 0 or 1 day, whereas number concentration of ultrafine particles showed the strongest effect on cardiovascular mortality with a lag of 4–5 days.

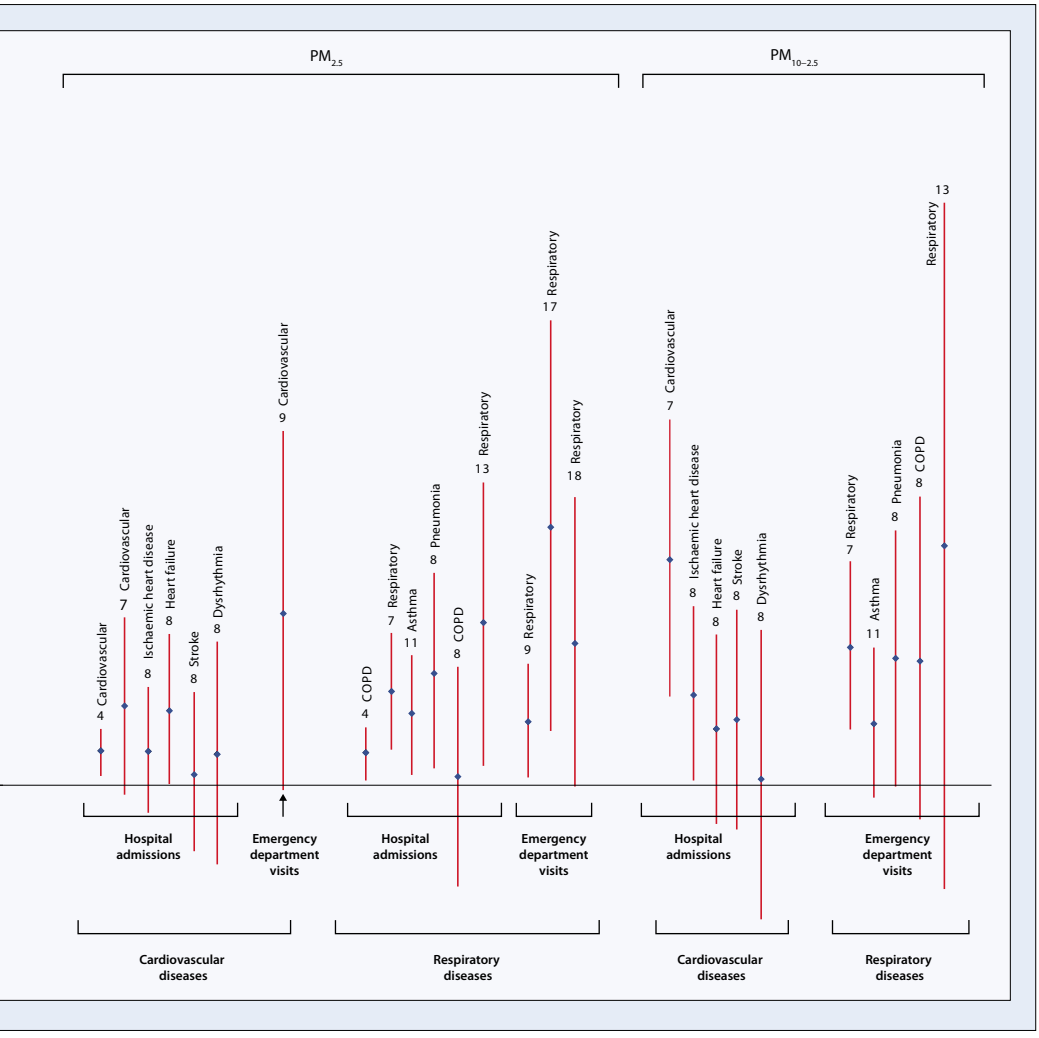
The size distribution in the range 0.01–2.5 μm was investigated by Peters et al. in Erfurt, Germany, in 1992 in a study on adult asthmatics *(325)*. For the health outcomes of cough and peak expiratory flow rate, the estimated effect of five-day mean of the number count for ultrafine particles was larger than for the mass of fine particles. Pekkanen et al. reported similar changes in peak flow, to be correlated to several sizes of PM, including ultrafine particles. Pekkanen

Fig. 3. Excess risk estimates for hospital admissions and emergency department visits for cardiovascular and respiratory diseases in single-pollutant models from Canadian and United States studies, including aggregate results from one multi-city study



Note. PM increments: 50 µg/m3 for PM10 and 25 µg/m3 for PM2.5 and PM10–2.5. Results presented from time series studies that did not use a generalized additive model (GAM) or were re-analysed using a generalized linear model (GLM).
Source: US Environmental Protection Agency *(4)*.

1. Zanobetti & Schwartz *(302)*, 14 United States cities
2. Linn et al. *(303)*, Los Angeles
3. Moolgavkar *(275)*, Cook County
4. Moolgavkar *(275)*, Los Angeles
5. Schwartz & Morris *(304)*, Detroit
6. Morris & Naumova *(305)*, Chicago
7. Burnett et al. *(306)*, Toronto
8. Ito *(280)*, Detroit
9. Stieb et al. *(307)*, St John
10. Schwartz *(308)*, Detroit
11. Sheppard *(309)*, Seattle
12. Nauenberg & Basu *(310)*, Los Angeles
13. Thurston et al. *(311)*, Toronto
14. Tolbert et al. *(312)*, Atlanta
15. Lipsett et al. *(301)*, Santa Clara County
16. Choudhury et al. *(313)*, Montreal
17. Delfino et al. *(314)*, Montreal
18. Delfino et al. *(315)*, Montreal



et al. showed a decrease in peak flow in association with ultrafine particles but not with fine particles *(326)*. von Klot et al. *(327)* found in adult asthmatics that asthma medication use increased in association with fine and ultrafine particle concentrations. The effects were more delayed (0–14 days) and stronger for those on anti-inflammatory medication than for those on bronchodilators (0–5 days).

Pekkanen et al. showed an association between two-day lagged concentrations of $PM_{2.5}$ and of ultrafine number concentrations and an increased risk for ischaemia during exercise in male patients with coronary artery disease in Helsinki *(326)*. These two effects were independent of each other when tested in

two-pollutant models. In 131 patients with coronary artery disease, de Hartog et al. showed associations between $PM_{2.5}$ and cardiopulmonary symptoms such as shortness of breath and avoidance of activities *(328)*. Effects for ultrafine particles were generally weaker, but achieved statistical significance for the avoidance of activities. Henneberger et al. found associations between PM and ultrafine number concentrations and prolonged and inhomogeneous repolarization of the heart *(329)*. These changes indicated an increased risk of arrhythmia and the associations were observed with particle exposures six hours before the electrocardiogram recordings were made.

In myocardial infarction survivors in five European cities, von Klot et al. found an increased risk for readmission to hospital due to cardiac causes to be associated with PM_{10} concentrations on the same day as well as estimated particle number concentrations on the same day *(330)*. An immediate effect of fresh combustion products was also suggested in a study linking time spent in traffic with onset of myocardial infarction one hour later *(331)*.

Taken together, the above-mentioned studies suggest that ultrafine particles may induce adverse health effects immediately, with a 2–4-day lag, and in association with cumulative exposures. This is consistent with the different potential mechanisms proposed for ultrafine particles, which include activation of irritant receptors within the airways, translocation of ultrafine particles, and subsequent endothelial cell activation and increased thrombogenicity. In most of the studies, effects were seen with both PM and ultrafine particle number concentrations, indicating that PM and particle number concentrations characterize different properties of the ambient aerosol.

Biomass

Given the importance of biomass combustion to global population exposure, especially resulting from indoor combustion in developing countries (Chapter 9), this chapter also considers the evidence specifically associating exposure to PM arising from biomass combustion with adverse health impacts. Further, as discussed previously, large-scale vegetation fires may also result in very high concentrations of particles over large geographical areas. In contrast to the large amount of information relating particles in urban air to health impacts, there are only a limited number of studies directly evaluating the community health impacts of air pollution resulting from the burning of vegetation and other biomass fuels. Several reviews have discussed the health impacts and pollutants associated with ambient wood smoke air pollution *(332,333)*. Although the emphasis of these reviews was on community exposures resulting from burning of wood in fireplaces and wood stoves, many of the conclusions are relevant to the broader understanding of air pollution from vegetation fires. WHO has sponsored a publication entitled *Health guidelines for vegetation fire events (334)*, which also contains a review of evidence associating air pollution from vegetation fires with

human health effects. Health impacts associated with residential indoor exposures in developing countries have also been reviewed in detail *(335)*.

Residential combustion in developed countries

In some locations, especially in colder climates during winter, wood combustion for residential heating is an important source of exposure to PM. Several studies indicate that wood stoves, especially older models, can emit smoke directly into the home *(333)*. Newer, airtight stoves emit less smoke into the home, but indoor exposure still occurs owing to infiltration back into the home of smoke emitted to the outside. Therefore, while these earlier studies strongly suggest that there are adverse impacts associated with wood smoke exposure, their crude exposure assessment precludes more specific conclusions.

A case–control study conducted among Navajo children evaluated the association between wood smoke exposure and acute lower respiratory illness (ALRI) *(336)* and revealed an increased risk of ALRI for children living in households that cooked with any wood or had indoor particle concentrations greater than or equal to 65 $\mu g/m^3$. The indoor particle concentration was positively correlated with cooking and heating with wood (geometric mean levels of approximately 60 $\mu g/m^3$) but not with other sources of combustion emissions *(336)*.

Several other studies have evaluated health outcomes in communities where wood smoke is a major, although not the only, source of ambient PM *(337)* and measured reduced lung function during the wood-burning season and in areas affected by wood smoke. In one study *(333,338)*, lung function was measured in 326 (including 24 asthmatics) elementary school children before, during and after two wood-burning seasons in an area of Seattle in which 80% of particles are from wood smoke *(333)*. Fine particulates were measured continuously with an integrating nephelometer. Significant lung function decrements were observed in the asthmatic subjects in association with increased wood smoke exposure. The highest (night-time 12-hour average) $PM_{2.5}$ level measured during the study period was approximately 195 $\mu g/m^3$ and PM_{10} levels were below the US National Ambient Air Quality Standard of 150 $\mu g/m^3$ during the entire study period *(339)*. For the asthmatic children, FEV_1 and FVC were estimated to decrease by 17 and 18.5 ml, respectively, for each 10-$\mu g/m^3$ increase in $PM_{2.5}$, while significant reductions in lung function were not observed in the non-asthmatic children.

A companion study, evaluating the impact of PM on emergency department visits for asthma in Seattle *(340)*, found a significant association between PM_{10} particle levels and emergency department visits for asthma. The authors indicate that, on an annual basis, 60% of the fine particle mass in Seattle residential neighbourhoods is from wood burning. Two time series studies have been conducted in Santa Clara County, California, an area in which wood smoke is the single largest contributor to winter PM_{10}, accounting for approximately 45% of winter PM_{10}. PM levels are highest during the winter in this area. The first study was one of the

initial mortality time series studies, which indicated an association between relatively low PM_{10} levels and increased daily mortality *(341)*. A study of asthma emergency department visits in Santa Clara County and winter PM_{10} found a consistent relationship. Specifically, a 10-μg/m^3 increase in PM_{10} was associated with a 2–6% increase in emergency department visits *(342)*.

Estimates for Christchurch, New Zealand, indicate that more than 90% of winter PM pollution in that city is emitted from biomass combustion *(343)*. In this setting, hospital admissions were associated with increased PM_{10}, the concentration of which during the study period averaged 25 μg/m^3, with a maximum of 283 μg/m^3. The results were stratified into total cardiac and total respiratory admissions. The estimated increases in admissions for the interquartile range (14.8 μg/m^3) for all age groups were 1.26 (CI 0.3–2.2) for cardiac admissions and 3.37 (CI 2.3–4.4) for respiratory admissions *(343)*.

Residential combustion in developing countries

The effects on health of inhaling biomass smoke have been documented in developing countries where women, and in some cases children, spend many hours cooking over unvented indoor stoves. These studies are reviewed in Chapter 9 and in more detail elsewhere *(92,93,335)*. Only a fraction of the studies directly measured PM exposures. For example, a case–control study conducted in Zimbabwe found a significant association between lower respiratory disease and exposure to wood smoke pollution in young children. Air sampling in the kitchens of the homes of 40 children indicated very high concentrations (546–1998 μg/m^3) of respirable particles *(344)*. In addition to the risks posed to infants, women who are cooking are also at risk of chronic respiratory diseases. In Maputo, Mozambique, exposure measurements made when four types of fuel (wood, charcoal, electricity and liquefied petroleum gas (LPG) were used for cooking indicated that wood users were exposed to significantly higher levels of particulate pollution during cooking (1200 μg/m^3) than those using other fuels. Wood users were found to have significantly more cough symptoms than other groups, although other respiratory symptoms such as dyspnoea, wheezing and breathing difficulties were not associated with wood use *(345)*. For comparison with other studies, the wood-burning group had 69 hour-years of exposure *(346,347)*.

Vegetation fires

Several studies in North America have evaluated the health impacts associated with forest and brush fires. Duclos and colleagues *(348)* evaluated the impact of a number of large forest fires in California on visits to emergency departments. During the approximately 2½-week period of the fires, visits for asthma and COPD increased by 40% and 30%, respectively. PM_{10} concentrations as high as 237 μg/m^3 were measured. In a retrospective evaluation of the health impacts of a large wildfire in a northern California Indian reservation, visits to the local

medical clinic for respiratory illness increased by 52% over the same period the previous year *(349)*. During the ten weeks that the fire lasted, PM_{10} levels exceeded 150 μg/m^3 (24-hour average) 15 times, and on two days the levels exceeded 500 μg/m^3. Weekly concentrations of PM_{10} were strongly correlated with weekly visits for respiratory illness during the fire year (r = 0.74), but not in the previous year (r = –0.63). In a community survey of 289 respondents, more than 60% reported respiratory symptoms during the smoke episode; 20% reported symptoms persisting for at least two weeks after the smoke cleared. Individuals with pre-existing cardiopulmonary diseases reported significantly more symptoms before, during and after the fire than those without such illnesses.

More recently, Sutherland and colleagues *(350)* reported an increase in an index of respiratory symptoms (dyspnoea, cough, chest tightness, wheezing and sputum production) among a panel of 21 subjects with COPD associated with two days of elevated ambient particle levels resulting from a forest fire near Denver. On the two days in which symptom scores were increased, average $PM_{2.5}$ concentrations increased to 63 μg/m^3 compared with an average of 14 μg/m^3 on control days.

Studies of Australian bushfires have not reported consistent associations between particle concentrations and emergency department visits for asthma *(351–353)*, although one recent study did observe an association between daily visits for asthma (adjusted for influenza and day-of-week effects) and measured PM_{10} during bushfire smoke episodes, especially for days in which PM_{10} concentrations exceeded 40 μg/m^3 *(354)*.

Major regional episodes of air pollution from vegetation fires in South-east Asia have been the subject of several investigations and surveillance programmes, and indicate increases in emergency department visits for asthma during such "haze" periods *(355)*. Reports from surveillance monitoring activities conducted during major South-east Asian episodes in 1997 and 1998 also indicated effects on health care utilization. In Singapore, for example, there was a 30% increase in hospital attendance for "haze-related" illnesses, and a time series analysis indicated that a PM_{10} increase of 100 ug/m^3 was associated with 12%, 19% and 26% increases in cases of upper respiratory tract illness, asthma and rhinitis, respectively. This analysis did not observe any significant increases in hospital admissions or mortality *(356)*. Similar findings were also observed in Malaysia *(33,34,357,358)*. Only one study has evaluated the impact of air pollution from vegetation fires on mortality. Sastry *(359)* evaluated the population health effects in Malaysia during this same episode. In this analysis, a 10-μg/m^3 increase in PM_{10} measured in Kuala Lumpur was associated with 0.7 % (all ages) and 1.8% (age 65–74 years) increases in adjusted relative risk of non-traumatic mortality, effect estimates that are similar to those reported from urban air pollution studies.

Agricultural burning

Agricultural burning is also an important seasonal source of ambient particles in many (especially rural) areas of the world. In one of the few studies of an urban population exposed to air pollution from agricultural burning, 428 middle-aged subjects with slight-to-moderate airway obstruction were surveyed for their respiratory symptoms during a two-week period of exposure to straw and stubble combustion products *(360)*. During the exposure period, 24-hour average PM_{10} levels increased from 15–40 μg/m^3 to 80–110 μg/m^3, with corresponding increases in carbon monoxide and volatile organic compounds. While 37% of subjects were not bothered by smoke at all, 42% reported that symptoms (cough, wheezing, chest tightness and shortness of breath) developed or became worse due to the air pollution episode and 20% reported that they had trouble in breathing. Subjects with asthma and chronic bronchitis were more likely to be affected, and women appeared to be more susceptible than men for several symptoms (cough, shortness of breath, nocturnal awakening) *(360)*. This study indicates that other forms of biomass air pollution, in addition to wood smoke, are associated with some degree of impairment, and suggests that individuals with pre-existing respiratory disease may be particularly susceptible.

Rice stubble burning has been the subject of several specific investigations, given the importance of rice as a global food crop *(361)*. A recent study in Iran evaluated the relationship between rice stubble burning and respiratory morbidity, especially asthmatic symptoms *(362)*. During a burning period lasting several weeks, PM_{10} concentrations doubled and significant increases were noted in the prevalence of asthmatic and other respiratory symptoms in a study population of 994 residents of an agricultural region. Among symptomatic individuals, pulmonary function was also reduced during the burning period.

Thus, there is strong evidence from the available literature that PM from biomass combustion is associated with a range of adverse health impacts, and little evidence to suggest reduced or altered toxicity from these particles relative to the more commonly studied urban air PM. Although the majority of studies have focused on respiratory health outcomes, in contrast to the emphasis on cardiovascular effects from urban and regional particle exposure, this does not imply that exposures to biomass particles do not result in adverse cardiac effects.

Evaluation

Exposure evaluation

There are substantial data on ambient PM exposures of people throughout the world. The relevant data come from exposure models, monitors sited for regulatory purposes, and more focused research studies that may incorporate personal exposure measurement. These studies confirm that ambient PM makes a substantial contribution to personal exposure to PM; that exposures occur at a broad

range of concentrations (some well above regulatory limits); and that the ambient PM to which people are exposed is a diverse mixture. There are numerous sources of ambient PM, comprising both particles released directly from combustion sources and those formed secondarily through complex chemical reactions. The complex characteristics of ambient PM have challenged researchers as they have attempted to characterize PM sources and exposures.

As this chapter discusses, major advances have been made in understanding the relationship between actual human exposure and ambient concentration measurements. In developed countries, ambient particles are responsible for approximately 50% of an individual's total $PM_{2.5}$ exposure, with relatively little variability between different population subgroups (although with substantial within-group variability). In a developing country scenario with indoor biomass combustion and consequently much higher indoor exposures, the contribution of ambient particles, while still substantial, will be smaller. In the absence of indoor sources, indoor concentrations and consequently exposure to PM of ambient origin are largely determined by the air exchange characteristics of the indoor environment. On average, indoor concentrations of $PM_{2.5}$ of ambient origin are 40–70% of ambient $PM_{2.5}$ concentrations. With this improved understanding of the relationships between exposure and ambient concentrations, the extensive database on ambient concentrations can be reliably used for risk evaluation.

Health risk evaluation

The 2000 review *(1)* found evidence sufficient to link PM to a variety of adverse effects on mortality and morbidity, in both the short and the long term. It offered quantitative estimates of risks for selected outcomes, based on the epidemiological information. Subsequent evidence reaffirms the multiple associations of PM with adverse health effects and broadens the range of effects to more conclusively encompass cardiovascular outcomes. There is substantial new evidence from time series studies of daily mortality, particularly from multi-city studies that span Europe and North America. Methodological concerns about time series studies that surfaced since the previous review have been addressed, and major re-analyses of key time series studies have been completed. The cohort studies of mortality have been extended, and the findings of the two most critical studies validated through an extensive, peer-reviewed re-analysis. Many further studies of morbidity indicators have also been carried out.

The epidemiological evidence is supported by an increasingly strong foundation of toxicological research. Various mechanisms have been proposed by which PM may cause and/or exacerbate acute and chronic diseases. Inflammation due to the production of reactive oxygen species is emerging as a central mechanism. However, one of the most vexing research challenges has been identifying physical and chemical characteristics of PM determining toxicity, so that linkages can be made back to the sources of the most injurious particles. This review, along

with that carried out by the US National Research Council's Committee on Research Priorities for Airborne Particulate Matter, shows that specific characteristics cannot yet be identified as critical for toxicity, although research findings support several candidates, including ultrafine particles.

Exposure assessment research has also contributed to this necessary foundation for characterizing the risks of PM. The contribution of ambient PM to personal exposures has been characterized, affirming that ambient PM contributes substantially to personal exposures even though most time is spent indoors. The exposure assessment studies have also provided evidence supporting the use of ambient PM concentration as an indicator of population exposure to PM in epidemiological studies.

The evidence does not lead to the use of any specific indicator beyond either PM_{10} or $PM_{2.5}$, both size fractions of particles that enter the respiratory tract. USEPA is also proposing a new National Ambient Air Quality Standard for coarse particles in urban areas, representing the PM mass lying between 2.5 μm and 10 μm in aerodynamic diameter. This size fraction is captured by PM_{10}. The amount of material in this size fraction depends on the local source mix and meteorology.

There has long been evidence showing that high levels of PM and other pollutants adversely affect health. The air pollution disasters of the last century have provided incontrovertible evidence of the adverse consequences of PM and other pollutants. The more recent evidence reaffirms the adverse consequences of air pollution for population health and supports an independent role of PM in causing adverse health effects. This independent role has been documented through epidemiological studies that have carefully disentangled the effect of PM from the potentially confounding effects of other pollutants, and by toxicological studies that have demonstrated mechanisms by which PM may cause adverse health effects.

As the evidence on PM has grown over the last five years, it has convincingly demonstrated adverse effects at contemporary levels of exposure in cities in Asia, Europe, Latin America and North America. For various health outcomes, there has not been any indication of a threshold below which adverse effects would not be anticipated. The lack of an apparent threshold for adverse health effects poses a substantial barrier for proposing standards that protect the public against such effects. The evidence also excludes the possibility of implementing standards that would protect against adverse health effects with a high degree of certainty.

USEPA, in the face of evidence indicating that a standard cannot be set for PM with an "adequate margin of safety", has used risk assessment methods in considering the level at which the National Ambient Air Quality Standard for PM should be set *(4)*. The approach considers a number of locations and the impact of various scenarios of control for the estimated burden of disease. The

analysis is based on risk coefficients from the epidemiological studies and exposure information obtained via the Agency's monitoring network. It offers a potential model for broader application. Guidance on conducting an assessment of the health impacts associated with a given level of ambient PM can be found in Ostro *(363)*.

Some of the best documented quantitative relationships between PM concentration and the occurrence of selected adverse health effects are given in Table 5. These coefficients can be used, along with monitoring information on ambient PM concentrations, to estimate the burden of disease attributable to PM and the potential impact of various scenarios of control. Use of these risk relationships in any particular setting is subject to uncertainty related to their generalizability; on the other hand, there is not yet sufficient evidence to focus on specific PM fractions, whether defined by physical or chemical properties, for the purpose of standard setting.

Table 5. Risk estimates for PM exposure

Outcome	Source	Reference	Estimate	95% CI
Daily mortality (all-cause)	WHO meta-analysis	WHO *(2)*	0.6%/10 μg/m^3	0.4–0.8
Daily mortality (respiratory)	WHO meta -analysis	WHO *(2)*	1.3%/10 μg/m^3	0.5–2.09
Daily mortality (cardiovascular)	WHO meta -analysis	WHO *(2)*	0.9%/10 μg/m^3	0.5–1.3
Daily mortality (all-cause)	NMMAPS revised	Health Effects Institute *(243)*	0.21%/10 μg/m^3	0.09–0.33
Daily mortality (cardiovascular)	NMMAPS revised	Health Effects Institute *(243)*	0.31%/10 μg/m^3	0.13–0.49
Long-term mortality (all-cause)	ACS CPS II 1979– 1983	Pope et al. *(323)*	4%/10 μg/m^3	1–8
Long-term mortality (cardiopulmonary)	ACS CPS II 1979– 1983	Pope et al. *(323)*	6%/10 μg/m^3	2–10

Guidelines

The evidence on airborne PM and public health is consistent in showing adverse health effects at exposures experienced by urban populations in cities throughout the world, in both developed and developing countries. The range of effects is broad, affecting the respiratory and cardiovascular systems and extending to children and adults and to a number of large, susceptible groups within the general population. The risk for various outcomes has been shown to increase with exposure, and there is little evidence to suggest a threshold below which no adverse health effects would be anticipated. In fact, the lower range of concentrations at which adverse health effects has been demonstrated is not greatly above the

background concentration, which has been estimated at 3–5 μg/m^3 in the United States and western Europe for $PM_{2.5}$. The epidemiological evidence shows adverse effects of particles after both short- and long-term exposures.

Current scientific evidence indicates that guidelines cannot be proposed that will lead to complete protection against adverse health effects of PM, as thresholds have not been identified. Rather, the standard-setting process needs to achieve the lowest concentrations possible in the context of local constraints, capabilities and public health priorities. Quantitative risk assessment offers one approach for comparing alternative scenarios of control and estimating the residual risk with achieving any particular guideline value. USEPA and the European Commission have recently used this approach in making recommendations for revisions of the existing standards for PM. Countries are encouraged to consider an increasingly stringent set of standards, tracking progress through emission reductions and declining concentrations of PM. The numerical guideline values given in the tables provide guidance on the concentrations at which increasing and specified mortality responses due to PM are expected, based on current scientific insights. As mentioned, to the extent that health effects associated with ambient PM have been reported at relatively low ambient concentrations, and that there is substantial inter-individual variability in exposure and response in a given exposure, it is unlikely that any PM standard or guideline level will provide universal protection for every individual against all possible PM-related effects.

The choice of indicator for PM also merits consideration. The most recent and extensive epidemiological evidence is largely based on studies using PM_{10} as the exposure indicator. Further, at present the majority of monitoring data are based on measurement of PM_{10} as opposed to other PM metrics. As an indicator, PM_{10} comprises the particle mass that enters the respiratory tract and includes both the coarse (PM_{10}– $PM_{2.5}$) and fine ($PM_{2.5}$) particles considered to contribute to the health effects observed in urban environments. In most urban environments, both coarse- and fine-mode particles are likely to be prominent, the former primarily produced by mechanical processes such as construction activities, road dust resuspension and wind, and the latter primarily from combustion sources. The composition of particles in these two size ranges is likely to vary substantially across cities around the world, depending on local geography, meteorology and specific sources. Combustion of wood and other biomass can be a major source of outdoor air pollution as well, the resulting combustion particles being largely in the fine ($PM_{2.5}$) mode. Although few epidemiological studies exist comparing the relative toxicity of combustion from fossil fuel vs biomass, similar effect estimates have been reported over a wide range of cities in both developed and developing countries. Therefore, it is reasonable to assume generally similar effects of $PM_{2.5}$ from these different sources. In the developing world, large populations are exposed to high levels of combustion particles indoors, and the WHO air quality guideline for PM also applies to these situations.

PM_{10} is suggested as an indicator with relevance to the majority of the epidemiological data and for which there is more extensive measurement data throughout the world. However, as discussed below, the *numerical* guideline value itself is based on studies using $PM_{2.5}$ as an indicator, and a $PM_{2.5}$: PM_{10} ratio of 0.5 is used to derive an appropriate PM_{10} guideline value. This ratio of 0.5 is close to that observed typically in urban areas in developing countries and at the bottom of the range (0.5–0.8) found in urban areas in developed countries. If justified by local conditions, this ratio may be changed based on the local data when the local standards are set.

Based on known health effects, both short-term (24-hour) and long-term (annual) guidelines are needed for both of the PM indicators.

The annual average guideline value of 10 μg/m^3 for $PM_{2.5}$ was chosen to represent the lower end of the range over which significant effects on survival have been observed in the American Cancer Society (ACS) Study *(295)*. Adoption of a guideline at this level places significant weight on the long-term exposure studies using the ACS and Harvard Six Cities data *(248,290,293–295)*. In these studies, robust associations were reported between long-term exposure to $PM_{2.5}$ and mortality. The historical mean $PM_{2.5}$ concentration was 18 μg/m^3 (range 11.0–29.6 μg/m^3) in the Six Cities Study and 20 μg/m^3 (range 9.0–33.5 μg/m^3) in the ACS study. Thresholds were not apparent in either of these studies, although the precise period(s) and pattern(s) of relevant exposure could not be ascertained. In the ACS study, statistical uncertainty in the risk estimates becomes apparent at concentrations of about 13 μg/m^3, below which the confidence bounds significantly widen since the concentrations are relatively far from the mean. In the study by Dockery et al. *(293)*, the risks are similar in the cities at the lowest long-term $PM_{2.5}$ concentrations of 11 and 12.5 μg/m^3. Increases in risk are apparent in the city with the next lowest long-term $PM_{2.5}$ mean of 14.9 μg/m^3, indicating likely effects in the range 11–15 μg/m^3. Therefore, an annual concentration of 10 μg/m^3 would be below the mean of the most likely effects levels indicated in the available literature. Targeting a long-term mean $PM_{2.5}$ concentration of 10 μg/m^3 would also place some weight on the results of daily exposure time series studies examining relationships between $PM_{2.5}$ and acute adverse health outcomes. These studies have long-term (three- to four-year) means in the range 13–18 μg/m^3. Although adverse effects on health cannot be entirely ruled out even below that level, the annual average WHO guidelines represent levels that have been shown to be achievable in large urban areas in highly developed countries, and attainment is expected to effectively reduce the health risks.

Besides the guideline values, three interim targets (IT) were defined, which have been shown to be achievable with successive and sustained abatement measures. Countries may find these interim targets helpful in gauging progress over time in the difficult process of steadily reducing population exposures to PM.

As the IT-1 level, a mean $PM_{2.5}$ concentration of 35 μg/m^3 was selected. This level is associated with the highest observed values in the studies on long-term health effects and may also reflect higher but unknown historical concentrations that may be responsible for observed health effects. This level has been shown to be associated with significant mortality in the developed world.

The IT-2 interim level of protection is 25 μg/m^3 and places greater emphasis on the studies of long-term exposure associated with mortality. This value is above the mean value observed in these studies at which health effects have been observed, and is likely to be associated with significant impacts from both long-term and daily exposures to $PM_{2.5}$. Attainment of this IT-2 value would reduce risks of long-term exposure by about 6% (95% CI 2–11) relative to the IT-1 value. The IT-3 level is 15 μg/m^3 and places even greater weight on the likelihood of significant effects related to long-term exposure. This value is close to the mean concentrations observed in studies of long-term exposure and provides an additional 6% reduction in mortality risk relative to IT-2.

In addition to guidelines and interim targets for $PM_{2.5}$, WHO recommends guidelines and interim targets for PM_{10}. This is because coarse PM (the fraction between 10 and 2.5 μm) cannot be considered harmless, and having a $PM_{2.5}$ guideline alone would provide no protection against harmful effects of coarse PM. At the same time, the quantitative evidence on coarse PM is considered insufficient to provide separate guidelines. In contrast, there is a large literature on short-term effects of PM_{10}, which has been used as a basis for the development of the WHO air quality guidelines and interim targets (Table 6).

The 24-hour average values refer to the 99th percentile of the distribution of daily values, i.e. the fourth next highest value of the year. The frequency

Table 6. Air quality guideline and interim targets for PM: annual mean

Annual mean level	PM_{10} (μg/m^3)	$PM_{2.5}$ (μg/m^3)	Basis for the selected level
WHO interim target 1 (IT-1)	70	35	These levels are estimated to be associated with about 15% higher long-term mortality than at AQG levels.
WHO interim target 2 (IT-2)	50	25	In addition to other health benefits, these levels lower risk of premature mortality by approximately 6% (2–11%) compared to IT-1.
WHO interim target 3 (IT-3)	30	15	In addition to other health benefits, these levels reduce mortality risk by approximately another 6% (2–11%) compared to IT-2 levels.
WHO air quality guidelines (AQG)	20	10	These are the lowest levels at which total, cardiopulmonary and lung cancer mortality have been shown to increase with more than 95% confidence in response to $PM_{2.5}$ in the ACS study *(323)*. The use of the $PM_{2.5}$ guideline is preferred.

distribution of daily $PM_{2.5}$ or PM_{10} values is most often roughly log-normal. Depending on the specific characteristics of their sources and location, countries may find that either the 24-hour guidelines or ITs given in this document (Table 7) or the annual average values are more restrictive. When evaluating the WHO guidelines and interim targets, the annual average is suggested to take precedence over the 24-hour average since, at low levels, there is less concern about remaining episodic excursions. Meeting the guideline values for 24-hour mean should protect against peaks of pollution that would lead to substantial excess morbidity or mortality. It is recommended that countries with areas not meeting these guideline values undertake immediate action to achieve these levels in the shortest possible time.

Table 7. Air quality guideline and interim targets for PM: 24-hour mean

24-hour mean level [a]	PM_{10} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	Basis for the selected level
WHO interim target 1 (IT-1)	150	75	Based on published risk coefficients from multicentre studies and meta-analyses (about 5% increase in short-term mortality over AQG)
WHO interim target 2 (IT-2)	100	50	Based on published risk coefficients from multicentre studies and meta-analyses (about 2.5% increase in short-term mortality over AQG)
WHO interim target 3 (IT-3) [b]	75	37.5	About 1.2% increase in short-term mortality over AQG
WHO air quality guidelines (AQG)	50	25	Based on relation between 24-hour and annual PM levels

[a] 99th percentile (3 days/year).
[b] For management purposes, based on annual average guideline values, the precise number to be determined on the basis of local frequency distribution of daily means.

Multi-city studies of 29 cities in Europe *(6)* and 20 cities in the United States *(14,15)* reported short-term mortality effects for PM_{10} of 0.62% and 0.46% per 10 $\mu g/m^3$ respectively. A meta-analysis of 29 cities from outside western Europe and North America reported an effect of 0.5% *(29)*. A meta-analysis confined to Asian cities reported an effect of 0.49% *(28)*. This suggests that the health risks for PM_{10} are likely to be similar in cities in developed and developing countries, at around 0.5%. Therefore, a concentration of 150 $\mu g/m^3$ would relate to roughly a 5% increase in daily mortality, an impact that would be of significant concern and one for which immediate mitigation actions would be recommended. The IT-2 level of 100 $\mu g/m^3$ would be associated with an approximately 2.5% increase in daily mortality. The IT-3 level and air quality guideline for the 24-hour average for PM_{10} are 75 and 50 $\mu g/m^3$, respectively, and reflect the relationship between 24-hour and annual average discussed above.

In addition to $PM_{2.5}$ and PM_{10}, ultrafine particles have recently attracted significant scientific and medical attention. These are particles smaller than 0.1 μm

and are measured as number concentration. While there is considerable toxicological evidence of potential detrimental effects of ultrafine particles on human health, the existing body of epidemiological evidence is insufficient to reach a conclusion on the exposure–response relationship to ultrafine particles. Therefore no recommendations can be provided at present as to guideline concentrations of ultrafine particles.

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11. Ozone

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General description

Sources

Ozone (O_3) and other photochemical oxidants are pollutants that are not directly emitted by primary sources. Rather, they encompass a group of chemical species formed through a series of complex reactions in the atmosphere driven by the energy transferred to nitrogen dioxide (NO_2) molecules when they absorb light from solar radiation (represented in the equations below by hυ, where h is Planck's constant and υ is the frequency of light).

The precursors that contribute most to the formation of oxidant species in polluted atmospheres are nitrogen dioxide and non-methane volatile organic compounds (VOCs), especially unsaturated VOCs. Methane is much less reactive than the other VOCs but is present at much higher concentrations, having risen in concentration over the past 100 years owing to its increasing use as fuel, and is released from rice fields and farm animals. Photochemistry involving methane accounts for much of the rise in ozone over the oceans and remote land areas, from about 30 μg/m^3 to about 75 μg/m^3.

The simplified general equations that regulate atmospheric photochemistry may be summarized as follows.

Nitrogen dioxide dissociates to form nitric oxide (NO) and atomic oxygen:

$$NO2 + h\upsilon\ (\lambda \leq 430\ nm) \rightarrow NO + O \quad (1)$$

Atomic oxygen combines with molecular oxygen to form ozone:

$$O + O_2 \rightarrow O_3 \quad (2)$$

Ozone is decomposed by reacting with nitric oxide, forming nitrogen dioxide and molecular oxygen:

$$NO + O_3 \rightarrow NO_2 + O_2 \quad (3)$$

Thus, photochemical pollution occurs when the photostationary cycle described in equations 1–3 is altered, either by events that consume nitric oxide or, conversely, favour the production of nitrogen dioxide. The reaction of nitric oxide with atmospheric peroxides (RO_2) is the main cause of disturbance of the photochemical equilibrium, as presented in reaction 4:

$$NO + RO_2 \rightarrow NO_2 + RO \quad (4)$$

Atmospheric peroxides are formed by the oxidation of VOCs as represented in the equations below, which describe oxidation of an alkene:

$$RCHCHR + O \rightarrow RCH_2 + RCO \quad (5)$$

(generation of free radicals)

$$RCH_2 + O_2 \rightarrow RCH_2O_2 \quad (6)$$

(generation of peroxides)

$$RCH_2O + O_2 \rightarrow RCHO + HO_2 \quad (7)$$

(generation of aldehydes)

$$RCH_2O_2 + NO_2 \rightarrow RCH_2O_2NO_2 \quad (8)$$

(generation of organic nitrates)

Reaction 8 may be seen as a way of stabilizing nitrogen dioxide and transporting it over long distances (mainly in the form of peroxyacetyl nitrate), since this reaction can be reversed far away from the original source of nitrogen dioxide.

There are several classes of VOCs (hydrocarbons and related compounds) in the atmosphere, mainly in emissions from large urban centres and industrial areas. These increase the complexity of photochemical reactions, mainly in areas characterized by high solar radiation. Thus reactions 1–8 are depicted only to describe some of the pathways responsible for the production of compounds in the atmosphere that lead to the production of ozone, the most representative and toxic pollutant of the class of ambient oxidants. For those interested in more information about atmospheric photochemistry, there are introductory textbooks well suited to health professionals *(1,2)*.

The ambient concentration of ozone depends on several factors: sunshine intensity, atmospheric convection, the height of the thermal inversion layer, concentrations of nitrogen oxides and VOCs, and the ratio of VOCs to nitrogen oxides. The VOC : nitrogen oxides ratio most favourable to ozone formation lies in the range 4 : 1 to 10 : 1.

Occurrence in the air

Ozone exhibits a considerable spatial variation since, once formed, it travels with the prevailing wind *(3)*, tending to reach higher concentrations in suburbs and remote downwind locations or at higher altitudes *(4)*. This suggests that it is likely that the highest concentrations of ozone occur in areas that lack adequate instrumental analysis of this pollutant. This situation is particularly important in the vicinity of large urban conglomerates in developing countries, where people living on the outskirts of megacities are exposed to oxidants that, owing to the absence of proper monitoring, are at levels that exceed air quality guidelines.

In the United States there is a relatively high temporal correlation among ozone monitors, falling from 0.8 for those within a few kilometres of each other to 0.6 for those separated by up to 150 km, where it remains relatively constant up to about 400 km *(5)*.

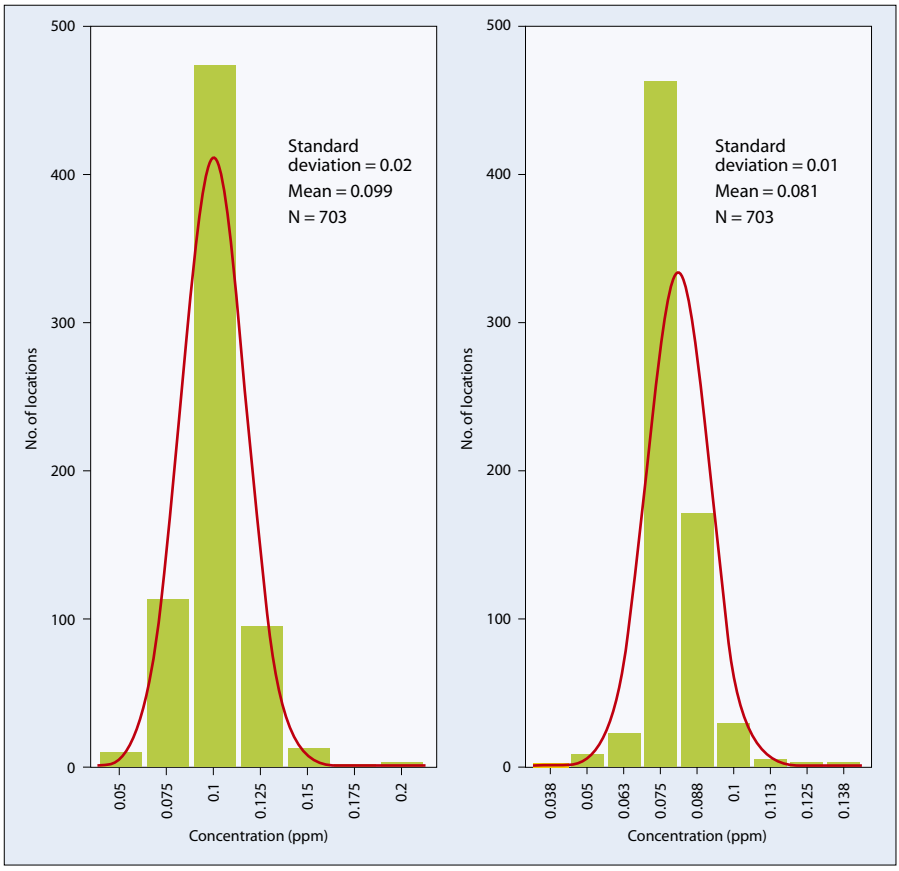
When trying to establish limits of ozone levels to preserve public health, it is also important to know how ambient concentrations relate to personal exposures, since indoor sources of ozone are rare. Personal exposures tend to correlate better with outdoor ozone during the summer months, but indoor ozone levels are significantly lower than those measured outdoors *(6)*. This suggests that the slope of the dose–effect relationships detected by epidemiological reports may underestimate the underlying exposure–response relationships. Studies in the United States provided substantial evidence that outdoor ozone concentrations are poor indicators of personal exposure *(4,6)*, whereas investigations in Mexico revealed significant indoor/outdoor correlations *(7,8)*. The most probable reasons for these differences are variations in housing, climate and the use of air conditioning systems, factors that influence the penetration of ozone into the indoor environment.

Taking into account the limitations involved in determining the relationship between ambient concentrations and the exposure of the affected population, it is important to know the ozone levels in densely inhabited areas. The monitoring networks covering the largest number of communities are located in North America and the EU. Fig. 1 was made using data provided by the US Environmental Protection Agency *(9)* and reports the maximum 1- and 8-hour ozone concentrations measured during the summer of 2003 in 703 communities. In general, the data display an approximately normal distribution. The mean and median 1-hour maximum concentrations in that period were similar and approach 200 $\mu g/m^3$.

For the same period (summer of 2003), Fig. 2 displays the distribution of the number of exceedances of the threshold value for informing the public (1-hour ozone concentration >180 $\mu g/m^3$) observed at rural and urban background stations in the European Community *(10)*.

The information given in Fig. 1 and 2 clearly indicates that progress in controlling ozone is slower than that for primary pollutants such as sulfur dioxide and carbon monoxide, even in areas of the globe that have resources and strict policies aiming to reduce air pollution. A worse picture can be drawn in developing countries, where the combination of megacities with significant emissions of ozone precursors and a climate that favours photochemical reactions produces higher levels of ozone compared with Europe and the United States. During the summer, for instance, the mid-afternoon levels of ozone in Latin American megacities such Mexico City and São Paulo may exceed 400 $\mu g/m^3$ for several days. In São Paulo, higher concentrations of ozone were detected downwind on the outskirts of the town, in areas with a high proportion of underprivileged people *(11)*.

Fig. 1. Frequency distribution of maximum 1-hour (left) and 8-hour (right) ozone levels measured during the summer of 2003 at 703 locations in the United States



Source: US Environmental Protection Agency *(9)*.

In fact, technically upgrading both light- and heavy-duty engines has resulted in a remarkable reduction in the levels of primary pollutants (except particles) in São Paulo, although the ozone levels are getting worse. This is due either to a reduction in nitric oxide levels or to the addition of ethanol to petrol (about 20–25% by volume) leading to an increase in precursors, mostly aldehydes. This later finding deserves attention, since the addition of oxygenated compounds to petrol is being considered by various countries. Thus it is likely that ozone will unfortunately remain a threat to public health in the coming years, in both developed and developing countries.

Ambient ozone concentrations are also affected by vertical mixing between the stratosphere and the troposphere. In general terms, ozone ascends from the troposphere to the stratosphere in the tropics, whereas the opposite occurs in temperate regions. Vertical mixing may accelerate considerably when boundary-layer air is lifted to the stratosphere in the core of cumulonimbus clouds.

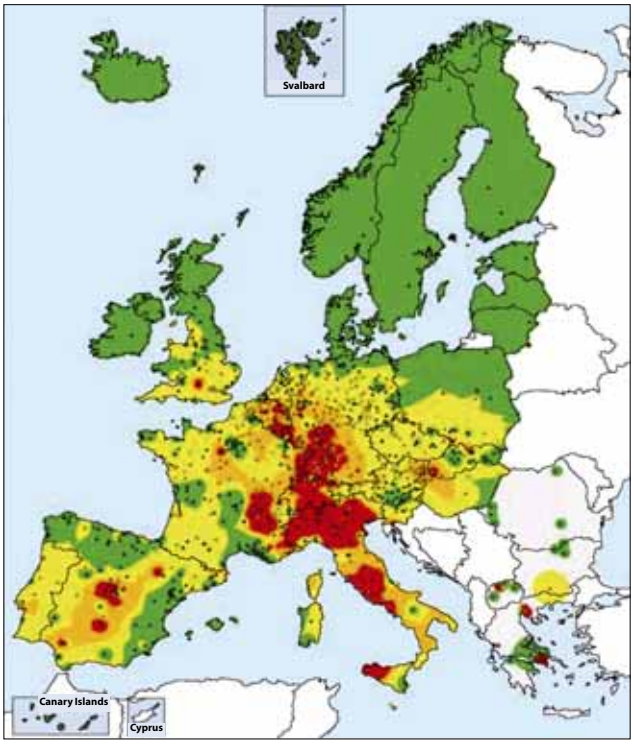


Fig. 2. Number of exceedances of the threshold value for informing the public at rural and urban background stations during the summer of 2003 in the EU, interpolated using inverse distance weighting

Source: van Aalst *(10)*.

Conversion factors for ozone:

1 ppm = 2 mg/m^3
1 mg/m^3 = 0.5 ppm

Route of exposure and toxicokinetics

Because of its high reactivity and low solubility in water, the half-life of ozone in liquid and solid media is negligible. Uptake of ozone is almost exclusively by inhalation, although there is evidence that some effects can be detected in the tear duct epithelial cells of individuals exposed to ambient ozone levels *(12)* and in murine skin (SKH-1 hairless mice) after exposure to 0.8 ppm for six hours per day for six days *(13)*. It is plausible that effects of ozone on skin are restricted to the upper layers of the dermis, and that no absorption occurs in its innermost compartments. Thiele et al. *(14)* demonstrated that exposure of mice to 10 ppm ozone for two hours significantly depleted vitamins C and E and induced malondialdehyde (MDA) formation in the upper epidermis, including the stratum corneum, but not in underlying layers. It is not known whether ambient levels of ozone induce significant oxidative stress to the skin to interfere with epidermal integrity and barrier function, thus predisposing to skin diseases.

Most ambient ozone absorption occurs in the upper respiratory tract and conducting intrathoracic airways *(15,16)*. Total ozone uptake is at least 75% in adult

males *(17)*. The rate of absorption may change, being inversely proportional to flow rate and increasing as tidal volume increases *(16)*. As tidal volume increases, there is a shift from nasal to oral breathing, with most of the inhaled air entering through the mouth at flow rates exceeding 40 litres per minute *(9)*. Since ozone removal in the upper respiratory tract is lower for oral than for nasal inhalation, ozone penetration into the lungs is much higher for people engaged in vigorous physical activity. Age and gender also influence ozone absorption, in quantity as well as topography, because of variations in airway size and the tissue surface of the conducting airways, which make absorption higher in children and females *(15)*.

Diffusion of ozone across the airway epithelial lining fluid (ELF) is determined by its reactivity. In fact, direct contact of ozone with airway epithelium seems to be small *(18)*. Indeed, the process by which ozone is retained along the respiratory tract may be characterized as "reactive absorption" *(19)*, whose rate is determined by the equilibrium constant of the chemical reactions between ozone and the constituents of ELF *(20)*. ELF contains substrates such as ascorbic acid, uric acid, glutathione, proteins and unsaturated lipids that may undergo oxidation mediated by ozone *(21)*, thus preventing (or minimizing) damage to the underlying epithelium. ELF is constantly renewed by the mechanical input provided by the coordinated movement of airway ciliated cells, producing new biological substrates to react with ozone and thus acting as a chemical barrier against this pollutant. Unfortunately, oxidation of some components of ELF may generate bioactive compounds, such as lipid hydroperoxides, cholesterol ozonization products, ozonides and aldehydes, with the potential to elicit inflammation and cell damage *(22)*.

The effectiveness of ELF in scavenging ozone, as well as the potential for the generation of toxic metabolites owing to the oxidation of ELF components and the possibility of direct interaction between ozone and respiratory tract cells, depends on several factors. Airflow velocity influences the interaction between ozone and ELF. Airflows above the critical Reynolds number will lead to turbulent flow, increasing the pressure driving ozone across ELF while, on the other hand, diminishing the time needed for chemical reactions between ozone and ELF. In fact, studies performed in isolated rat lungs demonstrated that ozone damage is greater during slow deep breathing than during rapid shallow respiration *(23)*.

The depth and chemical composition of ELF vary along the respiratory tract. In the rat, the depth of ELF ranges from 1 μm to 10 μm in the upper airways and has a high mucin content, whereas in distal airspaces ELF thickness drops by more than 0.5 μm and is composed primarily of elements of the surfactant system – lipids and proteins *(22,24)*. The geometry of the respiratory tract also has an influence on ozone toxicity. Modelling studies show that total percentage ozone uptake by the lungs is not markedly affected by age, but this changes when

the amount of ozone absorbed is normalized by regional surface areas of the different segments of the respiratory tract *(16)*. Malnutrition may interfere with the availability of antioxidant substances in ELF, such as vitamin E. Pre-existing pulmonary disease, such as chronic bronchitis, asthma or emphysema, leads to mechanical unevenness of airflow because of regional differences in the time constants of parallel respiratory units, thus interfering with the tissue dosimetry of ozone. Thus for any given ambient level of ozone concentration, its toxicity, preferential site of damage and pathogenetic mechanisms may vary depending on various factors in the human receptor.

Summary of the pathogenetic mechanisms of ozone toxicity

See Annex 1 for a full discussion of the extensive literature on this topic.

There are various mechanisms that mediate ozone-dependent injury.

- Short-term ozone inhalation induces a diffuse inflammation of the entire respiratory tract, although some parts of the airways are more susceptible: the nasal cavity and the transition zone between conducting and gas-exchange airways.
- Significant inflammation can be detected at ambient ozone levels, both in controlled human exposures and animal studies. Inflammation may be detected almost immediately after exposure by an increase in inflammatory mediators in bronchial lavage. Inflammatory cells are usually detected after a few hours.
- There is evidence that the acute inflammation induced by ozone is not restricted to the respiratory system, since markers of systemic inflammation – such as complement activation and increased protein synthesis by the liver – have been detected.
- Ozone affects pulmonary defences by several mechanisms: impairment of mucociliary clearance, decreased macrophage activity and effects on circulating lymphocytes. The effects on immunity are acute, and there is evidence of recovery with longer exposure (more than three days).
- Ozone causes bronchial hyperresponsiveness at ambient levels.
- There is some degree of adaptation to ozone after repeated exposures, owing to an increase in the antioxidant efficiency of the epithelial lining fluid of the airways as well as the release of eicosanoids and cytokines.
- Despite the reduced response to ozone after repeated exposures, pulmonary inflammation may persist, mainly in the terminal bronchiolar units.
- Longer exposures to ozone cause significant structural alterations to the lungs, characterized by diffuse mucus hyperplasia, bronchiolar narrowing and alveolar fibrosis. These alterations revert partially after finishing the exposure protocol.
- Pre-existing pulmonary disease, age and genetic factors influence susceptibility to injury.

- There is evidence that ozone induces mutations in respiratory cells, but the results concerning carcinogenicity are inconclusive.
- There is some evidence of neurotoxicity induced by ozone exposure.

Health effects

The discussion that follows focuses largely on concentration–response functions in human populations, which are critical determinants in the selection of air quality guidelines for the protection of public health. The discussion is organized into the following topics.

Acute responses

- pulmonary system effects
- cardiovascular system effects
- time series morbidity effects
- time series mortality effects.

Chronic effects

- reduced lung function
- development of atherosclerosis
- development of asthma
- reduction in life expectancy.

For the acute responses, other than the newly emerging area of cardiovascular function, there is a very large and rapidly growing literature that has been organized in a relatively uniform format with data summarized in tabular form. These tables are accompanied by a concise summary of the conclusions drawn by the WHO working group on the relevance of this information to the selection of a short-term ambient concentration guideline.

For acute cardiovascular function and all of the chronic effects, there is less published information, and that information is more difficult to summarize in a standardized or consolidated manner. For these discussions, therefore, each paper in the literature that bears significantly on the topic is described and discussed individually, prior to the presentation of an evaluation of the topic as a whole.

The health effects literature that, for the current review, has paramount influence on the selection of a short-term guideline is that on: (*a*) acute pulmonary system effects in human chamber exposure and field studies; and (*b*) time series studies on morbidity and mortality. Judgement is required in the interpretation of the pulmonary system effects, in that some of the measurable effects may not be worthy to be considered adverse. By contrast, any excess in hospital admissions and excess daily mortality attributable to ozone is clearly adverse. For the other categories of effects, there is currently some evidence that adverse effects could

be occurring but insufficient quantitative concentration–response evidence exists to serve as a basis for a long-term ambient concentration guideline.

Acute pulmonary system effects

Inflammation, reflexes, reduction of pulmonary defences and remodelling are processes triggered by ozone inhalation. It is plausible that ozone promotes adverse acute and chronic health effects. In this part of the chapter, acute effects are divided into three aspects: alterations of pulmonary function and inflammatory mediators; morbidity; and mortality. The tables in Annex 1 summarize key information on the most informative of the many studies in the literature.

Alterations in pulmonary function and inflammatory mediators

A very large number of studies on the acute effects of ozone exposure in humans have been performed, employing different experimental approaches: controlled exposures at rest or during exercise; single or continuous exposures; exposures at ambient levels; and evaluating the effects of ozone on subjects with pre-existing pulmonary disease such as asthma or chronic bronchitis. Table 1 of Annex 1 provides brief summaries of some representative papers on the acute effects of exposure on physiological parameters in humans.

The information contained in Table 1 of Annex 1 supports the following conclusions.

- There is solid evidence that short-term exposure to ozone impairs pulmonary function.
- Controlled exposures indicate that transient obstructive pulmonary alterations may occur for 6.6-hour exposures at ozone levels of 160 $\mu g/m^3$, a concentration frequently surpassed in many locations in the world.
- People with asthma and allergic rhinitis are somewhat more susceptible to transient alterations in respiratory function due to acute exposure to ozone.
- Changes in pulmonary function and depletion of airway antioxidant defences are immediate consequences of ozone exposure. Increase in inflammatory mediators, upregulation of adhesion molecules and inflammatory cell recruitment can be detected hours after exposure and may persist for days.
- Ozone enhances airway responsiveness in both healthy individuals and asthmatics.
- Studies conducted under field conditions, such as summer camps, have detected transient functional effects at ozone levels considerably lower than those observed in controlled exposures. Various factors may account for this discrepancy: concomitant exposure to other pollutants (including other components of the photochemical smog) and difficulties in precisely determining individual exposure (present and past). On the other hand, one has to consider that the lower threshold for adverse effects may be influenced by

the higher number of days of observation in such studies, thus increasing the power of detecting a significant effect.

Acute cardiovascular system effects

As discussed in Chapter 10, the effect of ambient air pollution on cardiovascular function and the initiation and progression of cardiovascular disease in laboratory animals and human populations is an emerging field of interest and of intense study. In studies of acute responses in humans, however, it is generally not possible to separate effects due to peaks in PM concentrations from those that may be due to ozone.

Park et al. *(25)* conducted a study of 603 men in the Boston, Massachusetts area who were enrolled in the Veterans Administration Normative Aging Study and underwent routine electrocardiographic monitoring, including measurement of heart rate variability (HRV). Reduced HRV is a well-documented risk factor for cardiac disease. Low-frequency HRV was reduced by 11.5% (95% CI 0.4–21.3) per 2.6 μg/m^3 increment in the previous 4-hour average of ozone, and the effect was stronger in men with ischemic heart disease and hypertension. There were also significant associations of HRV with PM_{10} levels.

Rich et al. *(26)* studied patients in the Boston area who had implanted defibrillators, and reported an increased risk of paroxysmal atrial fibrillation episodes associated with short-term increases in ambient ozone. The odds ratio for a 44-μg/m^3 increase in ozone during the hour before the arrhythmia was 2.1 (95% CI 1.2–3.5; $P = 0.001$). The associations with $PM_{2.5}$, nitrogen dioxide and black carbon were not significant.

These first studies of acute changes in cardiac function associated with ambient ozone exposures provide biological plausibility for the associations between cardiac morbidity and mortality and ozone level in the epidemiological studies reviewed in the following sections.

Morbidity

There is solid evidence that ozone acutely increases morbidity. Different health indicators were employed, although the majority of studies focused on respiratory conditions. School absenteeism, hospital admissions or emergency department visits for asthma, respiratory tract infections and exacerbation of chronic airway diseases were the most common health end-points.

School absenteeism due to respiratory events in kindergarten children living in the south-western part of Mexico City was positively associated (20% increase) with ambient levels of ozone >260 μg/m^3 for two consecutive days, the effect being amplified by low temperature *(27)*. In northern Nevada, absenteeism in elementary schools was estimated to increase by 13.01% (95% CI 3.41–22.61) for an increase of 100 μg/m^3 ozone *(28)*. In a study conducted in fourth-grade schoolchildren in 12 southern California communities, an increase of 40 μg/m^3 ozone

was associated with an increase of 62.9% (95% CI 18.4–124.1) in illness-related absence rates, 82.9% (95% CI 3.9–222.0) in respiratory illnesses, 45.1% (95% CI 21.3–73.7) in upper respiratory illnesses and 173.9% (95% CI 91.3–292.3) in lower respiratory illnesses with wet cough *(29)*. A time series study conducted in the Republic of Korea reported an increase in absenteeism in elementary school children in association with ozone (1.08 relative risk for an increase of 32 μg/m^3) *(30)*. The public health significance of excess school absence, and its impact on cost–benefit analyses for air pollution control effects, has been discussed by Künzli et al. *(31)*.

Tracking the severity of respiratory symptoms in asthmatic children is another approach to determining the acute health effects of ozone. In a study conducted in the New Haven, Connecticut area, ozone was significantly associated with respiratory symptoms in asthmatic children; a 100-μg/m^3 increase in 1-hour ozone was associated with increased likelihood of wheeze (by 35%) and chest tightness (by 47%) *(32)*. Within a cohort of 846 inner-city asthmatic children aged 4–9 years in seven American communities, an increase in ozone of 30 μg/m^3 was associated with a higher risk of morning symptoms (odds ratio = 1.16; 95% CI 1.02–1.30) and with a 0.59% decline in morning peak expiratory flow rates (PEFR) (95% CI 0.13–1.05) *(33)*. In the same population, children born prematurely or with low birth weight had greater declines in morning PEFR (1.8%) and a higher incidence of morning symptoms (odds ratio = 1.42) *(34)*. In a cohort of children with asthma in 12 southern California communities, respiratory symptoms were associated with the yearly variability of ozone (odds ratio = 1.06 per 2 μg/m^3; 95% CI 1.00–1.12).

There are large multi-city studies relating numbers of hospital admissions for respiratory diseases *(35)* and COPD *(36)* to ambient ozone levels. Such associations were robust enough to persist after controlling for temporal trends in admission rates, day-of-week and seasonal effects, gaseous and particulate air pollution, and climatic factors. Effects of ozone on respiratory admissions seem stronger during warmer weather. The results of some representative studies relating ozone to hospital admissions are briefly summarized in Table 2 of Annex 1. A smaller number of studies looked for associations between ambient ozone levels and cardiovascular conditions. Almost all the studies listed considered other pollutants in the analyses. The vast majority of the studies obtained positive and significant associations between variations in ambient ozone levels and increased morbidity. The effects were manifested among children, elderly people, asthmatics and those with COPD. The magnitude of the risk for respiratory morbidity associated to an increase of 20 μg/m^3 ozone ranged from none to 5% *(37)*. There is some evidence of a threshold in the dose–response functions relating ozone to respiratory disease, the lowest effect level being around 150 μg/m^3.

Ten of the 15 studies focusing on cardiovascular diseases in Table 2 of Annex 1 showed no significant effects of ozone. In addition, there is no clear positive

effect of ozone on any of the particular end-points evaluated (myocardial infarction, sudden death, stroke, congestive heart failure and peripheral arterial diseases). Thus, on the basis of the available information, it is clear that the effects of ozone on cardiovascular morbidity need further evaluation.

Mortality

The results of some representative studies relating ozone to mortality are briefly summarized in Table 3 of Annex 1. Significant associations were obtained for different causes, mainly respiratory and (to a lesser extent) cardiovascular. The effects of ozone on mortality were detected mostly in the elderly, and the studies focusing on mortality in children are not fully coherent. Interestingly, in Asia ozone was associated with mortality due to stroke *(38)*. The magnitude of the mortality risk exhibited a seasonal variation, being more intense in warmer weather. The range of relative risks of mortality due to respiratory diseases for an increase of 20 μg/m^3 ozone was between 0.23% *(39)* and 6.6% *(40)*, such variation depending on the age group, season of the year and model specifications. It is reasonable to postulate that adjusting the models for temperature plays a significant role in the magnitude of the coefficients relating ozone to mortality. The relationship between acute effects of ozone and mortality was reinforced by the recent publication of four meta-analyses *(41–44)*. These were consistent in showing a significant association between ozone and short-term mortality that was not substantially altered by exposure to other pollutants (including PM), temperature, weather, season or modelling strategy. Increases in total mortality have been observed at a concentration as low as 75 μg/m^3 (1-hour mean) *(42)*.

Chronic effects in humans

Ideally, an assessment of long-term effects of ozone in humans would include epidemiological studies investigating cumulative ozone exposure in association with three interrelated types of outcome, namely associations with: (*a*) early markers of chronic processes relevant to the development of diseases; (*b*) onset of asthma; and (*c*) death or reduction in life expectancy.

Early markers of chronic processes relevant to the development of diseases

Lung function

Measures of lung function have most often been used as an objective early marker of chronic pulmonary effects. Given the lifetime pattern of growth and decline in lung function, both cross-sectional and prospective studies can provide insights into the role of ozone exposure. The former approach has been used in children, adolescents and young adults. Prospective studies have been conducted in children and adolescents, focusing on lung function growth. Decline in lung function has not yet been investigated in relation to cumulative exposure to ozone.

The most thorough study is the Children's Health Study carried out in multiple cohorts in 12 communities in southern California *(45)*. The *cross-sectional* analyses indicated associations between lung function and annual means of daily 1-hour ozone maxima. An association with small airway function was particularly pronounced *(46)*. However, the findings were significant only among girls and in boys spending more time outdoors (FVC –128.6 (SE = 56) per 40 ppb; FEV_1 –136.3 (SE = 51.3)). For the same cohorts studied prospectively, lung function *growth rates* showed significant associations with a set of urban pollutants ($PM_{2.5}$, nitrogen dioxide and acid vapour), but findings for ozone were not significant and were inconsistent across age groups and lung function parameters *(47–49)*. Growth rates in small airway function – primarily expected to be associated with ozone – were inversely associated with ozone among the youngest cohort only *(48)* but not in the eight-year follow-up from age 10 to 18 *(49)*.

Several aspects are of interest. First, the study was limited to 12 communities with only a two-fold range in ambient ozone levels. Second, within-community variation in personal exposure (owing to differences in the use of air conditioners, ventilation patterns and time spent indoors) could not be fully controlled, and may be a source of noise or bias. Third, if chronic effects of ozone happened primarily in early life, one may expect discrepancies between cross-sectional results and those based on growth rates if the latter were observed after the susceptible period. Thus, null findings in the growth rate analyses do not necessarily contradict positive findings in the cross-sectional analysis.

Two studies carried out by the University of California at Berkeley (UCB) chose a powerful cross-sectional design to maximize lifetime exposure to ozone *(50,51)*. Instead of selecting (a limited number of) communities, UCB freshmen who had lived all their lives in California were invited to participate. The pilot study *(50)* included 130 and the main study *(51)* 255 non-asthmatic students. Ozone was interpolated on a monthly basis to each residential location over each student's lifetime. The integration of time–activity data into the exposure model did not affect the results. Both studies observed consistent and significant cross-sectional associations between individual lifetime ozone exposure and, in particular, small airway function, namely $FEF_{25–75}$ and FEF_{75} (but also FEV_1) at age 18–20. An increase of 2 $\mu g/m^3$ in lifetime 8-hour mean ozone was associated with 2.7% and 2.9% lower FEF_{75} in males and females, respectively *(51)*. The main study was large enough to investigate susceptible subgroups, and revealed that significant effects occurred only among students with small airways (marked by the ratio $FEF_{25–75}$/FVC) *(51)*. Effects were robust to adjustment for co-pollutants (PM and nitrogen dioxide).

Galizia & Kinney *(52)* employed a similar design, with individual assignment of long-term exposure to Yale (New Haven) College freshmen who had geographically diverse residential histories. FEV_1 and $FEF_{25–75}$ were significantly (and FEF_{75} borderline) associated with ozone exposure. $FEF_{25–75}$ was 8.11%

(range 2.32–13.9%) higher at the lowest than at the highest concentration (~300 μg/m^3, long-term mean of daily 1-hour maximum). Stratified analyses showed effects to be stronger in men but not significant in women. Another study addressing seasonal exposure was that of Ihorst et al. *(53)*, who made lung function measurements twice a year over 3½ years on 2153 schoolchildren in 15 towns in Austria and Germany. They concluded that ozone exposure may be related to seasonal changes in function growth, but significant changes in function growth were not detectable over 3½ years owing to partial reversibility or to the relatively low concentrations of ozone.

Atherosclerosis

A novel marker of chronic preclinical damage has been used to investigate effects of air pollution on atherosclerosis, measured by carotid intima-media thickness (CIMT) *(54)*. Systemic inflammatory responses to oxidant pollutants may contribute to atherogenesis. A Los Angeles study reported cross-sectional associations between CIMT and residential outdoor $PM_{2.5}$ levels, whereas associations with residential outdoor ozone were weak and statistically not significant *(55)*.

Onset of asthma

The onset of asthma (new diagnosis) was prospectively investigated in the Children's Health Study (CHS) *(56)* and in adults (AHSMOG study) *(57)*. The CHS followed more than 3500 non-asthmatic children aged 9–16 from 1993 to 1998. Community mean ozone level was not associated with new diagnosis of asthma. However, the number of outdoor sports engaged in by the children was correlated with asthma onset in communities with a high level of ozone. Playing three or more outdoor sports was associated with a relative risk of 3.3 (range 1.9–5.8) for developing asthma. In contrast, physical activity was not a risk factor for asthma in low-ozone communities *(56)*.

The 15-year follow-up of the Seventh Day Adventist Health Study (AHSMOG) cohort study included 3091 non-smoking adults *(57)*. As in the UCB studies, ozone levels were interpolated to residential locations to assign a 20-year exposure history to each subject. A 54 μg/m^3 change in long-term ozone was associated with a two-fold risk for asthma onset among men, though not among women. One may speculate that women spent more time indoors (where ozone levels are very low) or that protective hormonal factors may play a role. The interaction may also be a chance finding.

Cross-sectional retrospective assessments of symptom prevalence (e.g. wheezing) may not necessarily reflect long-term effects but rather the accumulated period prevalence of cumulative acute effects (such as acute exacerbations of asthma). Thus, retrospective studies are not reviewed here, as they cannot distinguish acute from chronic effects.

Death or reduction in life expectancy

Cohort mortality studies cannot unambiguously distinguish between (*a*) effects that lead to chronic processes and diseases that shorten life (i.e. chronic effects) and (*b*) acute or subacute effects of exposure that lead to death *(58)*. Cohort studies capture, at least in theory, both effects. Thus effects observed in cohort studies may not necessarily be solely due to *chronic* effects.

Several cohort studies have reported associations between long-term mean concentrations of ambient air pollutants and death rates, but results for ozone were not consistent, not as rigorously investigated as those for PM, or not reported at all. The American Cancer Society (ACS) study – the largest cohort of all – and the Harvard Six City study found no significant association of ozone with mortality *(59,60)*. The HEI re-analysis reported, however, a significant association of "warm-weather ozone" and cardiopulmonary mortality, with a relative risk (RR) of 1.08 (range 1.01–1.16) *(61)* and a significantly "protective" association for lung cancer. The recent extended analysis of the ACS cohort *(62)* observed increased mortality from cardiopulmonary diseases but not lung cancer associated with long-term summertime exposure to ozone. A more recent analysis conducted among ACS participants from southern California, however, observed no effect of long-term exposure on either cardiopulmonary disease or lung cancer mortality *(63)*. The two studies differ in that the southern California study based its exposure assignment on geospatially-derived estimates of residential concentrations, whereas the national study assessed exposure at an urban area level.

In the 15-year follow-up of the AHSMOG population, lung cancer was significantly associated with ozone level among men *(64)*. Associations were positive for other causes of death but not statistically significant.

Do we know the long-term exposure to ozone?

This question needs to be addressed in all the studies cited above. In contrast to pollutants such as PM, ozone is highly reactive. As a consequence, indoor/outdoor ratios are in general low and very heterogeneous across houses, locations and seasons. This spatio-microenvironmental heterogeneity is far more critical for ozone than for PM. Some studies conducted on the east coast of the United States suggest that ambient ozone concentrations may be very poorly associated with personal exposure (or dose), at least in some cities and/or seasons *(65,66)*. This has not been investigated in any of the locations of the chronic effect studies cited above.

Pollutants such as PM and related primary pollutants (e.g. nitrogen oxides) react with ozone, leading to (usually unmeasured) negative correlations between (personal) exposure to ozone and other pollutants. These other pollutants may also contribute to adverse health effects and the ability to observe the long-term effects of ozone may thus be a major methodological challenge, particularly if the exposure term used to characterize ozone exposure was less correlated with

personal ozone than might be the case for these other pollutants. Community-based single-monitor studies (i.e. with clustered study populations) are more affected by these sources of error and noise than subject-based designs with individual assignment of exposure, such as the UCB and ASHMOG studies.

The interaction of outdoor activity, ozone level and asthma observed in the CHS study (and possibly in men in the AHSMOG study) also indicates that time spent outdoors needs to be controlled in the exposure assessment. Given prevailing lifestyles, with >90% of time spent indoors with generally low concentrations, time spent outdoors (and in outdoor activity) becomes the most important determinant of exposure to high ozone levels.

The issue of thresholds of no effect has yet to be addressed in studies of chronic effects. Ozone is a natural constituent of the atmosphere and the lung is equipped with oxidant defence mechanisms, and one may speculate that some levels of no effect may exist. An early cross-sectional investigation with NHANES II data observed inverse associations of ozone, nitrogen dioxide and total suspended particulates with FVC and FEV_1 among people 6–24 years of age *(67)*. The pattern in these associations with ozone would support speculation about thresholds of no effect. The results were driven by data from Californian communities in the upper range of the ozone concentration distribution.

Conclusion of chronic effect studies

Evidence for the chronic effects of ozone has become stronger. Animal data and some autopsy studies indicate that chronic exposure to ozone induces significant changes in airways at the level of the terminal and respiratory bronchioli. The reversibility (or not) of such lesions is a point that deserves clarification. Epidemiological evidence of chronic effects is less conclusive, owing mostly to an absence of studies designed specifically to address this question and inherent limitations in characterizing exposure. The studies with the most efficient approaches and more individual assignment of exposure provide new evidence for chronic effects of ozone on small airway function and possibly on asthma. Substantial uncertainties remain, however, and need to be addressed in future investigations. The partly inconsistent patterns or lack of associations may originate from limitations in exposure assessment and/or from the inability to identify those most susceptible to the chronic effects of ozone. Uncertainties should not be interpreted as evidence of no adverse chronic effects following repeated daily and seasonal exposure to ozone.

Evaluation of human health risks

The determination of human health risks associated with ozone exposure has to take into account some basic principles.

- Data from human controlled exposures indicate that levels of ozone that may be experienced in several areas of the world induce significant functional and

biochemical alterations, mostly in the respiratory tract. The translation of these acute functional abnormalities to disease is not straightforward. However, although sequential exposures to ozone induce some degree of adaptation, it is plausible that multiple acute injuries may lead to permanent damage to the target organs.

- Epidemiological field studies, such as those conducted in summer camps or during exercise in open air, have disclosed significant detrimental respiratory changes in concentrations lower than those reported in controlled exposures. Whether these differences reflect experimental design or, conversely, are the result of inhaling a mixture of components generated by the atmospheric photochemical cycle (and not considered in the analysis) is a question still to be answered. If the second hypothesis is correct, ozone may be playing the role of a proxy variable representative of a family of photochemical components.
- Estimates of the size effect of ozone on acute morbidity and mortality are dependent on model specifications. It seems that such estimates are greatly influenced by the approach employed to control meteorological parameters, mainly temperature. Other important factors are age, pre-existing morbid conditions and the lag between exposure and determination of the health end-point. More recent studies considering larger series or several communities, or using other statistical approaches such as case-crossover design, have confirmed that ozone is indeed associated to acute adverse health effects, expressed either as morbidity or as mortality.
- The adverse effects of ozone on the respiratory tract, from the nasal passages to the gas-exchange areas, are unequivocal. Animal experiments, controlled human exposures, short-term effects measured during or after outdoor activity, and morbidity and mortality studies all agree and support such a conclusion. The evidence for cardiovascular effects is less conclusive.
- Since the human respiratory tract contains antioxidant defences, and it has been shown that such defences are consumed during ozone exposure, it is reasonable to propose the existence of a threshold in the dose–response functions relating ozone to adverse health effects. In other words, effects should occur only after the depletion of antioxidant defences. In fact, the concept of a threshold is supported by studies dealing with controlled exposures. In epidemiological studies, however, the evidence of a threshold is weaker. This is probably due to the fact that, although individual thresholds may exist, such thresholds have no meaning at the population level, since individual thresholds may differ. In other words, it is highly probable that it will be impossible to ensure a concentration of no effect in population studies, since factors such as age, pre-existing diseases, social and economic factors, habits and genetic factors will provide individuals in sufficient numbers to obscure the determination of a clear no-effect concentration.

- Determining the relationship between ambient levels and personal exposure is critical in epidemiological studies on the health effects of ozone. The indoor/outdoor ratio is not constant, being affected by the housing and cultural conditions of a given population. Such behaviour may be one explanation for the clearer determination of the effects of ozone during warmer weather, when infiltration is greater, people spend more time outdoors, and ambient measurements consequently reflect personal exposure more precisely.
- Evidence for the chronic effects of ozone is supported by human and experimental information. Animal data and some autopsy studies indicate that chronic exposure to ozone induces significant changes in airways at the level of the terminal and respiratory bronchioli. The reversibility (or not) of such lesions is a point that deserves clarification. Epidemiological evidence of chronic effects is less conclusive, owing mostly to an absence of studies designed specifically to address this question and inherent limitations in characterizing exposure. The studies with the most efficient approaches and more individual assignment of exposure provide new evidence for chronic effects of ozone on small airway function and possibly on asthma.

Guidelines

The second edition of *Air quality guidelines for Europe (68)* set the guideline value for ozone at 120 μg/m^3 for an 8-hour daily average. Since the mid-1990s there has been no major addition to the evidence from chamber studies or field studies. There has, however, been a marked increase in health effects evidence from epidemiological time series studies. Combined evidence from those studies shows convincing, though small, positive associations between daily mortality and ozone levels, independent of the effects of particulate matter. Similar associations have been observed in both North America and Europe. These time series studies have shown effects at ozone concentrations below the previous guideline of 120 μg/ m^3, without clear evidence of a threshold. Evidence from both chamber and field studies also indicates that there is considerable individual variation in response to ozone. In view of these considerations, there is a good case for reducing the guideline from the existing level of 120 μg/m^3. It is recommended that the air quality guideline for ozone be set at 100 μg/m^3 for a daily maximum 8-hour mean.

It is possible that health effects will occur below this level in some sensitive individuals. Based on time series studies, the number of attributable deaths brought forward can be estimated at 1–2% on days when ozone concentration reaches this guideline level.

There is some evidence that ozone also represents unmeasured toxic oxidants arising from similar sources. Measures to control ozone are also likely to control the effects of these pollutants.

Hemispheric background concentrations of tropospheric ozone vary in time and space but can reach average levels of around 80 μg/m^3. These arise from both

anthropogenic and biogenic emissions of ozone precursors and downward intrusion of stratospheric ozone into the troposphere. The proposed guideline value may occasionally be exceeded owing to natural causes.

There is some evidence that long-term exposure to ozone may have chronic effects but it is not sufficient to recommend an annual guideline.

As concentrations increase above the guideline value, health effects at the population level become increasingly numerous and severe. Such effects can occur in places where concentrations are currently high owing to human activity or during episodes of very hot weather.

As shown in Table 1, the 8-hour interim target 1 level has been set at 160 μg/m^3, at which measurable (though transient) changes in lung function and lung inflammation among healthy young adults have been demonstrated during intermittent exercise in controlled chamber tests. Some might argue that these responses may not be adverse and that they were seen only with vigorous exercise. These views are counterbalanced by the possibility that there are substantial

Table 1. Ozone air quality guideline and interim target

	Daily maximum 8-hour mean	Effects at the selected ozone level
High level	240 μg/m^3	Significant health effects; substantial proportion of vulnerable population affected.
WHO interim target 1 (IT-1)	160 μg/m^3	Important health effects; an intermediate target for populations with ozone concentrations above this level. Does not provide adequate protection of public health. ***Rationale*** • Lower level of 6.6-hour chamber exposures of healthy exercising young adults, which show physiological and inflammatory lung effects. • Ambient level at various summer camp studies showing effects on health of children. • Estimated 3–5% increase in daily mortality [a] (based on findings of daily time series studies)
WHO air quality guideline	100 μg/m^3	This concentration will provide adequate protection of public health, though some health effects may occur below this level. ***Rationale*** • Estimated 1–2% increase in daily mortality [a] (based on findings of daily time series studies) • Extrapolation from chamber and field studies based on the likelihood that real-life exposure tends to be repetitive and chamber studies do not study highly sensitive or clinically compromised people or children. • Likelihood that ambient ozone is a marker for related oxidants.

[a] Deaths attributable to ozone concentrations above an estimated baseline of 70 μg/m^3 (based on 0.3–0.5% increase in daily mortality for 10 μg/m^3 8-hour ozone).

numbers of people in the general population, including persons of different ages, pre-existing health status and co-exposures, who might be more susceptible than the relatively young and generally healthy subjects who were studied. Furthermore, chamber studies provide little evidence about repeated exposure. Exposure to 160 μg/m^3 is also likely to be associated with the same effects noted at 100 μg/m^3. Based on time series evidence, the number of attributable deaths brought forward can be estimated at 3–5% for daily exposures above the estimated background.

At concentrations exceeding 240 μg/m^3, important health effects are likely. This is based on findings from a large number of clinical inhalation and field studies. Both healthy adults and asthmatics would experience significant reductions in lung function, as well as airway inflammation, that would cause symptoms and alter performance. There are additional concerns about increased respiratory morbidity in children. Based on time series evidence, the number of attributable deaths brought forward can be estimated at 5–9% for daily exposures above the estimated background.

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12. Nitrogen dioxide

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General description

Many chemical species of nitrogen oxides exist, but the air pollutant species of most interest from the point of view of human health is nitrogen dioxide. Nitrogen dioxide is a reddish brown gas with a characteristic pungent odour. Nitric oxide spontaneously produces the dioxide when exposed to air. Nitrogen dioxide gas is a strong oxidant, and reacts with water to produce nitric acid and nitric oxide.

Nitrogen dioxide is an important atmospheric trace gas not only because of its health effects but also because: (*a*) it absorbs visible solar radiation and contributes to impaired atmospheric visibility; (*b*) it absorbs visible radiation and has a potentially direct role in global climate change; (*c*) it is, along with nitric oxide, a chief regulator of the oxidizing capacity of the free troposphere by controlling the build-up and fate of radical species, including hydroxyl radicals; and (*d*) it plays a critical role in determining ozone concentrations in the troposphere because the photolysis of nitrogen dioxide is the only key initiator of the photochemical formation of ozone, whether in polluted or in non-polluted atmospheres *(1,2)*.

Nitrogen dioxide is subject to extensive further atmospheric transformations that lead to the formation of strong oxidants that participate in the conversion of nitrogen dioxide to nitric acid and sulfur dioxide to sulfuric acid and subsequent conversions to their ammonium neutralization salts. Thus, through the photochemical reaction sequence initiated by solar-radiation-induced activation of nitrogen dioxide, the newly generated pollutants are an important source of organic, nitrate and sulfate particles currently measured as PM_{10} or $PM_{2.5}$. For these reasons, nitrogen dioxide is a key precursor of a range of secondary pollutants whose effects on human health are well-documented.

Sources

On a global scale, emissions of nitrogen oxides from natural sources far outweigh those generated by human activity. Natural sources include intrusion of stratospheric nitrogen oxides, bacterial and volcanic action, and lightning. However, because natural emissions are distributed over the entire surface of the earth, the resulting background atmospheric concentrations are very small. The major sources of anthropogenic emissions of nitrogen oxides into the atmosphere are

the combustion processes in stationary sources (heating, power generation) and in mobile sources (internal combustion engines in vehicles and ships).

In most ambient situations, nitric oxide is emitted and transformed into nitrogen dioxide in the atmosphere. Oxidation of nitric oxide by atmospheric oxidants such as ozone occurs rapidly, even at the low levels of reactants. Altshuller *(3)* calculated that 50% conversion of nitric oxide would take less than one minute at a nitric oxide concentration of 120 μg/m^3 (0.1 ppm) in the presence of an ozone concentration of 200 μg/m^3 (0.1 ppm). Consequently, this reaction is regarded as the most important route for atmospheric nitrogen dioxide production, other contributions coming from specific non-combustion industrial processes such as the manufacture of nitric acid, the use of explosives, and welding. Indoor sources include tobacco smoking and the use of gas-fired appliances and oil stoves. Thus, differences in the nitrogen oxides (nitric oxide and nitrogen dioxide) emissions of various countries are due mainly to differences in fuel consumption.

Occurrence in air

Annual mean nitrogen dioxide concentrations in urban areas throughout the world are generally in the range of 20–90 μg/m^3 (0.01–0.05 ppm) *(1,4–6)*. Urban outdoor levels of nitrogen dioxide vary according to the time of day, the season of the year and meteorological factors. Typical daily patterns include a low background level of nitrogen dioxide, upon which is superimposed one or two peaks of higher levels that correspond to rush-hour traffic emissions of nitrogen oxides. Hourly averages near very busy roads exceed 940 μg/m^3 (0.5 ppm) nitrogen dioxide *(7)*. Several studies have measured ambient concentrations in road tunnels in Europe and the United States *(8)* and have shown that personal exposures in vehicles using these tunnels can be high. For example, a range of 179–688 μg/m^3 nitrogen dioxide inside a car in a road tunnel during rush hour has recently been reported *(9)*. The maximum hourly mean value may be several times the annual mean *(1,10)*. Long-term monitoring activities during the 1960s and 1970s indicated an increase in concentrations of nitrogen oxides in many urban areas throughout the world *(11,12)*. It is known that nitrogen dioxide concentrations are highly correlated with population *(1)*, and population worldwide continues to grow.

Owing to the widespread use of unvented combustion appliances, nitrogen dioxide concentrations in homes may greatly exceed those found outdoors *(1, 13)*. The average nitrogen dioxide concentration over a period of several days may exceed 200 μg/m^3 (0.1 ppm) when unvented gas stoves are used for supplementary heating or clothes drying, or when kerosene (paraffin) heaters are used, but typically, means are lower *(1,14–16)*. Maximum brief concentrations in kitchens are in the range of 230–2055 μg/m^3 (0.12–1.09 ppm) during cooking *(17,18)*. The highest 15-minute concentration recorded for a home with an unvented gas space heater was 2716 μg/m^3 (1.44 ppm) *(19)*.

Conversion factors

1 ppm nitrogen dioxide = 1880 μg/m^3
1 μg/m^3 nitrogen dioxide = 5.32×10^{-4} ppm
1 ppm nitric oxide = 1230 μg/m^3
1 μg/m^3 nitric oxide = 8.13×10^{-4} ppm

Routes of exposure

In the environment, nitrogen dioxide exists as a gas. Thus, the only relevant route of exposure to humans is inhalation, whether the source is outdoor or indoor air. Exposures to nitrogen dioxide from occupational sources are relatively rare compared to those from outdoor or domestic indoor sources.

Kinetics and metabolism

Upon inhalation, 70–90% of nitrogen dioxide can be absorbed from the respiratory tract of humans, and this increases further with exercise *(20,21)*. A significant portion of the inhaled nitrogen dioxide is removed in the nasopharynx (about 40–50% in dogs and rabbits); thus, as exercise shifts towards mouth-breathing, an increased delivery of nitrogen dioxide to the lower respiratory tract can be expected *(1,4,5,22,23)*.

Mathematical modelling studies show that maximum exposure to nitrogen dioxide by the tissues of the lower respiratory tract is predicted to be at the junction of the conducting airways and the gas-exchange region of the lungs in humans, rats, guinea-pigs and rabbits. Although the actual tissue dose of nitrogen dioxide at a similar starting tracheal concentration differs across species, the shape of the exposure curves is similar. The region predicted to receive the maximum dose is that where the typical nitrogen-dioxide-induced morphometric lesion is observed in several species of animals. Using this mathematical model, it is predicted that, as tidal volume increases in humans (e.g. during exercise), the dose delivered to the gas-exchange region increases substantially more than that of the conducting airways *(24–26)*.

Experimental studies have shown that nitrogen dioxide or its chemical products can remain within the lung for prolonged periods. Nitric and nitrous acids or their salts have been observed in the blood and urine after exposure to nitrogen dioxide *(1,4,22,23)*.

Health effects

Effects on experimental animals

Nitrogen dioxide exerts a range of biological effects on experimental animals. These include effects on lung metabolism, structure, function, inflammation and host defence against pulmonary infections. However, because of the inherent differences between mammalian species, e.g. in their capacity to inactivate

nitrogen dioxide, exactly what exposures would lead to these effects in humans – or whether some effects occur at all – is not known. This is proving to be a major impediment that is limiting our understanding of whether, at ambient concentrations in humans, nitrogen dioxide is an inhalant toxicant or not, especially when present at low concentrations over a prolonged period in the indoor and outdoor environment. From mathematical modelling, the distribution of nitrogen dioxide deposition within the respiratory tract of rats, guinea-pigs, rabbits and humans appears to be similar *(24–26)*, but very little information is available on tissue response from different species to a given dose or concentration. Thus, from currently available animal studies it is known which toxic effects of nitrogen dioxide *might* occur in humans, but the effects that are *actually* caused by a specific inhaled doses or concentration of nitrogen dioxide are proving very difficult to deduce with any level of confidence.

Pulmonary metabolism

Although there are exceptions, most biochemical studies of the lung show effects only after acute or subchronic exposure to high levels of nitrogen dioxide exceeding 3160 μg/m^3 (2 ppm) *(1,4,5)*. A notable exception is the effect on lung lipid metabolism. Lipid peroxidation is increased in rats exposed to concentrations as low as 752 μg/m^3 (0.4 ppm) (continuous for 18 months) when thiobarbituric acid reactants are used as an indicator, and 75 μg/m^3 (0.04 ppm) (continuous for 9 months) when ethane exhalation is the indicator *(27,28)*. Effects on both lipid and antioxidant metabolism show a response pattern that depends both on concentration and duration of exposure *(29)*. Frequently observed features at higher nitrogen dioxide levels include the induction of lung oedema, an increase in antioxidant metabolism, an increase in lung enzymes associated with cell injury, and changes in lung lipids. Although not fully understood, these alterations may be early signs of cell lesions, which become manifest only at higher concentrations or upon longer exposure *(1,4,5,22,23)*.

Pulmonary structure

In the tracheobronchial and alveolar regions of the lung, nitrogen dioxide at concentrations as low as 640 μg/m^3 (0.34 ppm) results in replacement of the type I alveolar epithelial and ciliated epithelial cells with the more oxidant-resistant type II and non-ciliated bronchiolar (Clara) cells, respectively. Furthermore, the replaced cells exhibit alterations of their cytoplasm and hypertrophy after short exposure (10 days) to concentrations of nitrogen dioxide above 940 μg/m^3 (0.50 ppm), the significance of which is not known *(1,4,5,23)*.

Both the exposure regimen used and the time of exposure are important. In a subchronic study of lung lesions in rats, Rombout et al. *(30)* showed that the concentration (C) of inhaled nitrogen dioxide had more influence on epithelial metaplasia than exposure duration (time, T) when C × T was constant, and

that the effect of C was greater with intermittent than with continuous exposure. Other experiments have addressed the temporal pattern of nitrogen dioxide effects and found them to be complex *(1)*. For example, over a seven-day period, a wave of epithelial hyperplasia occurs, peaking around the second day *(31)*. Rombout et al. *(30)* showed that some nitrogen-dioxide-induced interstitial changes were still present two months after a one-month exposure ceased.

In mice, rats, dogs and monkeys, long-term exposure to nitrogen dioxide leads to emphysema-like structural changes, in addition to thickening of the alveolar capillary membrane, loss of ciliated epithelium and increases in lung collagen *(1,4,5,22)*. The US Environmental Protection Agency *(1)* has reviewed 23 research reports on nitrogen dioxide exposure and emphysema to determine whether the effects reported met the US National Heart, Lung, and Blood Institute definition for human emphysema *(32)*. Because the animal studies were of interest for the purposes of extrapolation to humans, it is important to know whether or not the more rigorous definition of human emphysema (which includes destruction of alveolar walls) is met. Many of the reports contained insufficient detail to permit an independent judgement as to whether "human-type" emphysema had occurred. However, three studies have reported convincing evidence of human-type emphysema following exposure to very high nitrogen dioxide levels relative to ambient concentrations: Haydon et al. *(33)* exposed rabbits to 15 040–22 600 $\mu g/m^3$ (8–12 ppm) for 3–4 months; Freeman et al. *(34)* exposed rats to 37 000 (reduced to 28 200 or 18 800) $\mu g/m^3$ (20, reduced to 15 or 10 ppm) for up to 33 months; and Hyde et al. *(35)* exposed dogs for 5½ years to a nitrogen dioxide–nitric oxide mixture containing nitrogen dioxide at a concentration of 1210 $\mu g/m^3$ (0.64 ppm) and nitric oxide at 310 $\mu g/m^3$ (0.25 ppm). In this last study, the dogs exhibited several decrements in lung function, which, when compared to controls, continued to deteriorate during a 2½-year post-exposure period in clean air and revealed changes analogous to human centrilobular emphysema. Studies undertaken to localize collagen deposition within the lung exposed ferrets to 940 or 18 800 $\mu g/m^3$ (0.5 or 10 ppm) nitrogen dioxide for 4 hours a day for 8 or 15 weeks. Increased lung collagen deposition was identified within the submucosa of the respiratory bronchioles, although this only achieved statistical significance in the 18 800-$\mu g/m^3$ (10-ppm) group *(36)*.

Pulmonary function

On repeated exposure to high concentrations of nitrogen dioxide (1880–9400 $\mu g/m^3$ (1–5 ppm) there is some evidence of disordered mechanics of breathing and ventilatory function. These effects include increased breathing frequency *(1,4,5,22)*, while subchronic exposures of <1880 $\mu g/m^3$ (<1.0 ppm) reduced lung distensibility and gas exchange *(1,4,5)*. The effect of exposure to either 940 or 18 800 $\mu g/m^3$ (0.5 or 10 ppm) nitrogen dioxide on tracer particle clearance from the airways of ferrets during postnatal respiratory tract development has also

been examined. Thoracic clearance was reduced in both exposure groups, but was not significantly different in the 940-μg/m^3 (0.5-ppm) group than in control animals exposed to clean air *(37)*.

Airway inflammation and responsiveness

As nitrogen dioxide is a free radical, it has the potential to deplete tissue antioxidant defences and, as a result, cause injury and inflammation. Data confirming this reactivity are outlined below.

The effects of short-term (24-hour) exposure to nitrogen dioxide on airway eosinophilic inflammation and bronchial hyperresponsiveness have been examined using a standard murine model of antigen bronchoprovocation and airway inflammation *(38)*. BALB/c mice were sensitized to ovalbumin and exposed to 3760 μg/m^3 (2.0 ppm) nitrogen dioxide prior to being challenged with ovalbumin as aerosol on days 13 and 14. Nitrogen dioxide was found to enhance epithelial damage, reduce mucin expression and increase baseline smooth muscle tone. Although a modest increase in airway neutrophilia was also detected, exposure was not associated with airway eosinophilia or with an increase in bronchial hyperresponsiveness.

At even greater concentrations, the inflammatory response to nitrogen dioxide has been studied in a rat inhalation model using continuous exposure to 18 800 μg/m^3 (10 ppm) for 1, 3 and 20 days, with particular focus on the activation state of alveolar macrophages *(39)*. Whereas the number of inflammatory cells and total protein concentration in bronchoalveolar lavage (BAL) fluid were increased, tumour necrosis factor-alpha (TNF-α) was markedly reduced with increasing exposure time. In contrast, interleukin (IL)-10, IL-6 and suppressor of cytokine signalling-3 protein were elevated. Furthermore, in vitro lipopolysaccharide stimulation of BAL cells revealed a reduced ability to produce TNF-α, IL-1 β, and nitric oxide but a markedly increased transcription and protein release for IL-10. In addition, elevated levels of IL-6, scavenger receptor B and suppressor of cytokine signalling-3 mRNA were detected in BAL cells from exposed animals. Analyses of highly purified alveolar macrophages indicated that changes in the activation state of these cells were most probably responsible for the observed effects.

Host defence

Several types of animal study have indicated that nitrogen dioxide increases lung susceptibility to bacterial and perhaps viral infections *(1,4)*. The most extensive set of data was collected using an infectivity model that measures the total antibacterial defences of the lungs of mice. For long-term exposures, the lowest concentration tested that had an effect was 940 μg/m^3 (0.5 ppm) for six months of exposure (*4*0). After a three-hour exposure, the lowest concentration tested with an effect was 3760 μg/m^3 (2 ppm) *(41)*. Continuous exposure to concentrations ranging from 52 640 μg/m^3 to 940 μg/m^3 (from 28 ppm to 0.5 ppm) resulted in

linear, concentration-related increases in mortality due to pulmonary infection *(42)*. Additional studies have shown that the increase in mortality is highly dependent on the exposure regimen. Concentration would appear to be more important than duration of exposure in increasing susceptibility to infection.

These and other data show that peak exposures and patterns of exposure are important in determining response *(1,43,44)*. Some studies indicate that several months of exposure to nitrogen dioxide levels of approximately 940 μg/m^3 (0.5 ppm) can increase susceptibility to other bacteria and viruses, and that acute exposure to higher levels can decrease pulmonary bactericidal activity and alveolar macrophage function. In summary, it is clear that the effects of nitrogen dioxide are due more to concentration than to duration of exposure or to total dose (expressed as C × T), that differences in species sensitivity exist, that the lowest effective concentration of nitrogen dioxide also depends on the microbe used in the test, and that low levels cause effects only after repeated exposures *(1,4,5,22)*. Extrapolation of these findings to humans cannot be made directly, because most of the studies used pneumonia-induced mortality as an endpoint. However, the infectivity model reflects alterations in the defence mechanisms of mice that are shared by humans. This, together with other mechanistic studies, implies that the specific host defences of humans (such as alveolar macrophages) can be influenced by nitrogen dioxide. However, the quantitative relationship between effective nitrogen dioxide levels in animals and in humans is unknown. Although numerous studies provide evidence of the effects on the systemic humoral and cell-mediated immune systems, these studies are difficult to interpret *(1,4)*.

At the time of writing, there are no reports that nitrogen dioxide causes malignant tumours or teratogenesis *(1,4,45)*. Limited genotoxicity studies have produced mixed results with in vitro and high-concentration in vivo studies (e.g. 50 000 μg/m^3; 27 ppm) *(46)*. Extrapulmonary effects have also been observed but cannot be interpreted with respect to human risk *(1)*. Numerous studies of the interaction of nitrogen dioxide with other air pollutants, predominantly ozone, show that the effects are due to ozone alone, are additive, or are synergistic, depending on the end-point and exposure regimen *(30)*.

In vitro studies

The effects of nitrogen dioxide have been investigated using a variety of in vitro test systems. Exposure of human blood plasma to 26 230 μg/m^3 (13.95 ppm) nitrogen dioxide resulted in a rapid loss of ascorbic acid, uric acid and protein thiol groups, in addition to lipid peroxidation and a depletion of alpha-tocopherol (vitamin E) *(47)*. In a separate study, exposure to nitrogen dioxide over a lower concentration range (94–1880 μg/m^3; 0.05–1.0 ppm) resulted in the antioxidant defences, uric acid and ascorbic acid being depleted in human BAL fluid *(48)*. More recently, Olker et al. showed that superoxide radical release from BAL cells isolated from nitrogen-dioxide-exposed rats (18 800 μg/m^3 (10 ppm) for 1, 3 or

20 days) is significantly impaired *(49)*. This was explained by decreased production, as a consequence of an inhibition of NADPH oxidase and complex III of the respiratory chain and, to a lesser extent, increased scavenging brought about by enhanced glutathione peroxidase and copper/zinc-superoxide dismutase mRNA expression and enzyme activities.

The effects of nitrogen dioxide on various cell culture systems have also been described. One system exposed cultured human bronchial epithelial cells to 7520 and 15 040 μg/m^3 (4.0 and 8.0 ppm) nitrogen dioxide and elicited both cell membrane damage and increased membrane permeability *(50)*. It should be remembered that confluent airway epithelial cell monolayers in vitro are not fully differentiated and posses a markedly lower level of resistance to pollutants compared to the epithelium in the intact human. However, in a more physiologically relevant system, nitrogen dioxide (200 and 800 μg/m^3; 0.1 and 0.43 ppm) has also been shown to trigger inflammation in cultured human nasal mucosa explants using histamine release into the culture medium as a marker of the inflammatory response *(51)*. The early pro-inflammatory responses following exposure to a brief high concentration of nitrogen dioxide (84 600 μg/m^3; 45 ppm) have also been assessed using human bronchial epithelial cells as an in vitro model of inhalation injury *(52)*. While immunofluorescence studies confirmed oxidant-induced formation of 3-nitrotyrosine, the nitrogen-dioxide-exposed cells exhibited marked increases in the levels of nitrite (used as an index of nitric oxide), IL-8, IL-1β and TNF-α. Furthermore, in order to simulate a pre-existing "inflammatory" condition of the bronchial epithelium, such as would exist in asthma and other hyperreactive airway diseases, cells were pre-treated with various pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β and IL-8) for 24 hours prior to exposing them to nitrogen dioxide. The combination of cytokine treatment and nitrogen dioxide exposure consistently enhanced the generation of nitric oxide and IL-8.

Reproductive effects

A recent study examined effects in the rat of fetal exposure to diesel-engine exhaust containing nitrogen dioxide (1504 or 188 μg/m^3; 0.80 or 0.10 ppm) with or without PM (1.71 or 0.17 mg/m^3) on testicular cell numbers and daily sperm production in adulthood *(53)*. The mature rats that were exposed to diesel exhaust during the fetal period (from gestational day 7 to delivery) showed a reduction in the daily production of sperm owing to an insufficient number of Sertoli cells. All exhaust-exposed groups showed almost the same reactions toward the inhalation, indicating that the gaseous phase must have included the responsible toxicants; these were not identified, although nitrogen dioxide would be a major constituent.

Overall, acute exposures (hours) to low levels of nitrogen dioxide have rarely been observed to cause effects in animals. Subchronic and chronic exposures

(weeks to months) to such levels, however, cause a variety of effects, including alterations to lung metabolism, structure and function, inflammation and increased susceptibility to pulmonary infections. Emphysema-like changes involving destruction of alveolar walls have been reported only at very high nitrogen dioxide concentrations. It is apparent from both in vitro and animal toxicological studies that the potential for human health effects is broad. However, at present it is difficult to extrapolate quantitatively from animals to humans, with any degree of confidence, effective pollutant concentrations that exert toxicity.

Controlled human clinical studies

Pulmonary function

In general, during acute controlled exposures, concentrations of nitrogen dioxide in excess of 1880 μg/m^3 (1.0 ppm) are necessary to induce changes in pulmonary function in healthy adults (*1,4,5,23,54–58*). For example, significant increases in airway resistance have been reported on exposure to 9400 μg/m^3 (5.0 ppm) nitrogen dioxide *(58)*, whereas other studies have been unable to find any effects on lung function despite an exposure concentration as high as 7000 μg/m^3 (3.72 ppm) *(56)*. Since these concentrations almost never occur in ambient air, examination of the effects of nitrogen dioxide has focused on people with pre-existing lung disease.

Numerous studies on people with asthma, chronic obstructive pulmonary disease (COPD) or chronic bronchitis have shown that exposure to low levels of nitrogen dioxide can cause small decrements in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) or increases in airway resistance (R_{aw}) (Table 1). Asthmatics are the most responsive group to nitrogen dioxide studied to date, although controlled studies on the effects of short-term exposure on the symptoms and severity of asthma have not led to clear-cut findings (Table 1). It should be noted that most of the asthmatic volunteers had only a "mild" level of disease according to the US National Heart, Lung, and Blood Institute classification *(1)*, while there have been no studies of nitrogen dioxide in patients with severe disease or marked bronchial hyperresponsiveness.

The lowest level of nitrogen dioxide exposure reported in more than one laboratory to show a *direct* effect on pulmonary function in asthmatics, when exposed for 2–2½ hours, was 560 μg/m^3 (0.3 ppm) *(59–61)*. However, these results were not consistent. For example, no pulmonary function response was found in subjects exposed to concentrations of 1880–7520 μg/m^3 (1.0–4.0 ppm) for 1 or 1¼ hours using 15-minute cycles of exercise and rest *(56,62,63)* and, within the same laboratory, results have not been replicated with different groups of asthmatic patients *(59,64)*. Similar but statistically non-significant trends have been observed in other controlled human studies performed at concentrations of 230 and 188 μg/m^3 (0.1 ppm) for 20 or 60 minutes *(55,65,66)*. However, the small size of the decrements and concerns expressed over the level of statistical significance

Table 1. Controlled studies of the effects of nitrogen dioxide in people with pre-existing disease

Concentration ($\mu g/m^3$)	Concentration (ppm)	Exposure duration and activity	Number, sex and age of subjects
Asthmatics			
188	0.1	1 hour	20 M, 34 F (18–51 years)
188	0.1	1 hour	15 M (21–46 years)
188 752	0.1 0.4	1 hour	4 M, 6 F (16–60 years)
203–462 + 103–613 $PM_{2.5}$ + 61–218 PM_{10}	0.11–0.25	30 min	10 M, 10 F (19–54 years)
207 490	0.11 0.26	1 hour	13 M, 7 F (15–44 years)
207 (132–300)	0.11 (0.07–0.16)	1 hour	6 M, 1 F (mean: 31.1 years)
225 225 338	0.12 0.12 0.18	1 hour 40 min (10 min exercise at 33 litres/min) 40 min (10 min exercise at 30 litres/min)	4 M, 6 F (12–18 years) 4 M, 6 F (11–19 years) 7 M, 3 F (12–18 years)
230 460 910	0.12 0.24 0.48	20 min	6 M, 2 F (17–45 years)
260 140 1015	0.14 0.27 0.54	30 min	8 M, 12 F (17–56 years)
376	0.2	2 hours (1 hour exercise at 20 litres/min)	12 M, 19 F (18–55 years)
470	0.25	30 min	10 M, 4 F (20–55 years)
470	0.25	30 min (10 min exercise at 30 litres/min)	9 M, 2 F (18–55 years)
488	0.26	30 min exercise	19
490	0.26	30 min	9 M, 9 F (18–50 years)
500	0.27	30 min	10 M, 6 F (31–52 years)
500	0.27	30 min	6 M, 7 F (23–39 years)

Effects	Reference
No effect on specific airway conductance (SG_{aw}), FEV_1 or reactivity to ragweed. Variable effect (non-significant trend) on carbachol reactivity.	Ahmed et al. *(73,74)*
No effects on function or metacholine response.	Hazucha et al. *(65,75)*
No effect on FEV_1 . 752 µg/m^3 increased early (P <0.009) and late (P <0.02) response (decline in FEV_1) to house dust mite allergen.	Tunnicliffe et al. *(76)*
Subjective symptoms not pronounced. Increased specific R_{aw} (SR_{aw}) (P = 0.025) and thoracic gas volume (P = 0.01) following allergen exposure. Lower lung function (P = 0.04) and more asthma symptoms (0.016) during late phase.	Svartengren et al. *(77)*
At 207 µg/m^3, 13 out of 20 subjects had increased carbachol reactivity. At 490 µg/m^3, 1 out of 4 had increased reactivity.	Orehek et al. *(66)*
No change in SR_{aw} or grass pollen reactivity in three allergic asthmatics and four allergic subjects.	Orehek et al. *(78)*
At rest, no functional effects. With exercise, slight (P <0.06) decrease in FEV_1 at 338 µg/m^3.	Koenig et al. *(79–81)*
No change in SR_{aw}. Increase in histamine reactivity in 5 out of 8 subjects at 910 µg/m^3.	Bylin et al. *(54)*
Decline in SR_{aw} over time unrelated to nitrogen dioxide. Tendency to increased histamine reactivity in 14 out of 20 subjects at 140 µg/m^3 only.	Bylin et al. *(82)*
No effects on spirometry or SR_{aw}. Variable increase in metacholine reactivity.	Kleinman et al. *(83)*
No effect on SR_{aw}. Increased reactivity to sulfur dioxide.	Jörres et al. *(84)*
Mouthpiece exposure. No effects on metacholine reactivity.	Jörres et al. *(85)*
No affect on SR_{aw}, but thoracic gas volume was significantly reduced (P = 0.001) 5 hours after exposure. Bronchial responsiveness to histamine was significantly increased (P =0.03) 5 hours after exposure. Increased expression of an adhesion molecule (Mac-1) on granulocytes 30 min after exposure.	Strand et al. *(86)*
No effect on SR_{aw} or thoracic gas volume or early asthmatic reaction to birch or timothy pollen and histamine. During late response decreased peak expiratory flow (P = 0.016) and FEV_1 (P = 0.06). No effect on differential cell counts or eosinophil cationic protein.	Strand et al. *(87)*
No effect on function. Enhanced early (P = 0.02) and late (P = 0.01) airway response (decline in FEV_1) to birch or grass pollen. Tendency towards increased night-time symptoms after nitrogen dioxide and allergen (P = 0.07).	Strand et al. *(88)*
No effect on symptoms or function. Nitrogen dioxide and birch or timothy pollen enhanced percentage of neutrophils in bronchial wash (P = 0.05) and BAL (P = 0.02) and increased eosinophil cationic protein in bronchial wash (P =0.02).	Barck et al. *(89)*

▶

Concentration ($\mu g/m^3$)	Concentration (ppm)	Exposure duration and activity	Number, sex and age of subjects
▶ 500	0.27	15 min on day 1, 2 x 15 min on day 2	10 M, 8 F (23–48 years)
560 1130	0.3 0.6	2 hours (1 hour exercise at 40–41 litres/min)	27 M, 32 F (18–50 years)
560	0.3	2.5 hours (1.5 hours exercise at 30 litres/min)	24 M, 10 F (10–16 years)
560	0.3	0.5 hour (10 min exercise at 30 litres/min)	15 (20–45 years)
560 1880 5640	0.3 1.0 3.0	1 hour (30 min exercise at 41 litres/min)	15 M, 6 F (20–34 years)
560	0.3	225 min (30 min exercise at 30–40 litres/min)	10 M, 10 F (19–54 years)
560 282 560 1130	0.3 0.15 0.30 0.60	110 min (1 hour exercise at 42 litres/min) 75 min (30 min exercise at 42 litres/min)	13 M (19–35 years) 21 (19–30 years)
560	0.3	30 min (20 min exercise at >30 litres/min)	5 M, 4 F (23–34 years)
560 +/– combustion by-products 1130 +/– combustion by-products	0.3 0.6	1 hour	2 M, 7 F (19–65 years) 6 M; 5 F (7–15 years)
940	0.5 + 0.3 sulfur dioxide	2 hours (1 hour exercise at >20 litres/min)	7 M, 12 F (mean: 33 years)
940	0.5	1 hour	10 (22–44 years)
940	0.5	21 (15 min exercise)	9 M, 4 F (>71 years)
7520	4.0	75 min (15 min exercise at 25 or 49 litres/min)	12 M, 11 F (18–34 years)
COPD patients			
560	0.3	225 min (21 min exercise at 25 litres/min)	13 M, 7 F (47–70 years)
560	0.3	4 hours (exercise)	13 M, 7 F
752 +/– concentrated ambient particles	0.4	2 hours (15 min exercise every half hour)	9 M; 9 F (mean: 72 years)

Effects	Reference
No effect on SR_{aw}, FEV_1 or thoracic gas volume. No effect on neutrophils or eosinophils in blood or sputum, but increase in eosinophil cationic protein in blood ($P = 0.01$) and sputum ($P = 0.04$) and increase in blood myeloperoxidase ($P = 0.003$) post nitrogen dioxide plus birch or timothy pollen.	Barck et al. *(90)*
No significant effects on SR_{aw}. Possible increased cold air response at 560 µg/m^3 only.	Avol et al. *(91)*
At 60 min, decrease in FEV_1, FVC and peak expiratory flow. Increase in SR_{aw}. No change in cold air response. No effects after 2.5 hours' exposure.	Avol et al. *(61)*
No effect at rest. Nitrogen dioxide increased cold air response.	Bauer et al. *(60)*
No effects on function or reactivity to cold air.	Linn et al. *(62)*
No group change in function, symptoms or carbachol reactivity. However, previously studied subjects (19) had possible nitrogen dioxide responses.	Morrow & Utell *(64)*
Decreased FEV_1 after first 10 min of exercise; smaller change later. No effect on FEV_1 or SR_{aw}. No change in metacholine reactivity 2 hours after exposure.	Roger et al. *(59)*
No effect on function, SR_{aw}, reactivity to sulfur dioxide or symptoms.	Rubinstein et al. *(92)*
No effect on symptoms or function. Increase in airway hyperresponsiveness (post histamine) after exposure to 1130 µg/m^3 (minus combustion by-products) ($P = 0.006$).	Salome et al. *(57)*
No effect.	Linn et al. *(93)*
No symptoms. No functional changes. Decreased metacholine reactivity.	Mohsenin *(94)*
No effects.	Kerr et al. *(95)*; Kulle *(96)*
No effect on SR_{aw}, symptoms, heart rate or skin conductance. Small decrease in systolic blood pressure.	Linn & Hackney *(63)*
Decreased in FVC (after exposure) and FEV_1 (after >4-hour exposure).	Morrow & Utell *(64)*
Progressive decrements in FVC and FEV_1. Subgroup analyses suggested responsiveness decreased with severity of COPD.	Morrow et al. *(72)*
No effect on function, symptoms, spirometry or total or differential cell counts of induced sputum cells.	Gong et al. *(97)*

▶

Concentration (μg/m³)	Concentration (ppm)	Exposure duration and activity	Number, sex and age of subjects
940	0.5	2 hours (15 min at 25 litres/min)	7 (24–53 years) chronic bronchitics
940 1880 3760	0.5 1.0 2.0	1 hour (30 min exercise at 16 litres/min)	13 M, 9 F (48–69 years) 6 chronic bronchitics, 21 emphysemics, 4 asthmatics
940–9400	0.5–5	15 min	88 chronic bronchitics
1880–9400 9400	1–5 5	30 breaths (15 min) 1 hour	84 M (30–72 years) COPD patients
1880–15 040	1–8	5–60 min	130 (25–74 years): 116 COPD patients, 14 chronic bronchitics

of some of these results suggest that great caution should be exercised in accepting these findings as demonstrating acute effects.

In concentration–response studies, Von Nieding and colleagues *(67–70)* found that brief exposures to levels of 3000 μg/m³ (1.6 ppm) increased R_{aw} in people with COPD. No responses were seen, however, at similar concentrations in mildly exercising subjects exposed for one hour *(71)*. Longer exposures (4 hours) caused functional effects with COPD at lower levels (560 μg/m³; 0.3 ppm), and in healthy elderly subjects the nitrogen-dioxide-induced reduction in FEV_1 was greater among smokers than among those who had never smoked *(72)*.

The reasons for the conflicting findings observed with nitrogen dioxide inhalation in volunteers are unclear, but indicate that nitrogen-dioxide-induced increases in airways resistance at ambient concentrations may not show the expected monotonic concentration–response relationship *(54)*. Other possible explanations include differences in methods, subject selection (e.g. diagnosis of asthma and COPD, genetic variations in susceptibility) and the low statistical power of studies with small numbers of subjects.

Another parameter used to demonstrate the detrimental effect of nitrogen dioxide on pulmonary function is mucociliary activity, where a significant reduction was shown after healthy subjects were exposed to 2820–6580 μg/m³ (1.5–3.5 ppm) for 20 minutes *(98)*.

Pulmonary symptoms

There were no significant symptoms in either asthmatics or healthy subjects exposed to <1880 μg/m³ (<1.0 ppm) nitrogen dioxide. Symptoms have been provoked in healthy subjects exposed to 7520 μg/m³ (4.0 ppm) but not in asthmatics exposed to the same concentration *(63)*.

Effects	Reference
No effects in bronchitis alone. Possible decrease in quasistatic compliance.	Kerr et al. *(95)*
No change in spirometry. SR_{aw} tended to increase after first exercise period. No symptom change. No change in arterial oxygen saturation.	Linn et al. *(71)*
Decreased earlobe oxygen tension above 7520 μg/m^3. Increased R_{aw} above 3000 μg/m^3.	Von Nieding et al. *(68,69)*
Increased R_{aw} above 2820 μg/m^3. Decreased earlobe oxygen tension.	Von Nieding et al. *(70)*
At 7520–9400 μg/m^3 for 15 min, decreased arterial oxygen pressure. At ≥3000 μg/m^3, increased R_{aw}.	Von Nieding & Wagner *(67)*

Airway responsiveness

Based on the importance of bronchial hyperresponsiveness in the pathophysiology and clinical manifestations of asthma, considerable effort has been directed towards evaluating the effect of nitrogen dioxide on airways responsiveness to pharmacological, physical (e.g. cold air) or natural (e.g. allergens) bronchoconstrictor stimuli. In normal volunteers, concentrations of nitrogen dioxide >1880 μg/m^3 (>1.0 ppm) are required to detect any increased bronchial responsiveness in healthy adults *(1,4)*. Consequently, greater emphasis has been placed on the responses of people with pre-existing lung disease, such as asthma and COPD, who have elevated baseline nonspecific airways responsiveness (Table 1).

Cold-induced airway constriction and bronchial responsiveness to histamine in asthma are potentiated by nitrogen dioxide at concentrations of 560 μg/m^3 (0.3 ppm) and 488 μg/m^3 (0.26 ppm), respectively *(68,82)*. Others have reported a possible increase in reactivity to cold air at 560 μg/m^3 (0.3 ppm) but not at 1130 μg/m^3 (0.6 ppm) *(91)*, with no such effect in a follow-up study *(61)*. No enhancement of allergen-reduced responsiveness was found in asthmatics on exposure to nitrogen dioxide, but this may be because of the low levels of nitrogen dioxide used (190 μg/m^3; 0.1 ppm) *(73–78)*. A meta-analysis of 20 bronchoconstrictor studies of asthmatics and 5 studies of normal subjects revealed a statistically significant increase in airways responsiveness to a range of constrictor stimuli on exposure to ≥200 μg/m^3 (≥0.11 ppm) nitrogen dioxide in asthmatics and to ≥1900 μg/m^3 (≥1.01 ppm) in controls *(99)*.

More recent studies have investigated the effect of pre-exposure to nitrogen dioxide to enhance the asthmatic response to inhaled allergen in sensitized subjects. Exposure to 800 μg/m^3 (0.43 ppm) nitrogen dioxide enhanced the bronchoconstrictor response of patients with mild asthma to inhaled house dust mite allergen *(76)*. A similar effect was seen when subjects with allergic asthma were

exposed to 500 μg/m^3 (0.27 ppm) followed by inhalation of pollen allergen *(87)*, and also after repeated exposure to 500 μg/m^3 (0.27 ppm) nitrogen dioxide in combination with a non-symptomatic allergen dose *(88)*. In an attempt to understand the mechanism of the enhancing effect of nitrogen dioxide on the asthmatic reaction to allergen, Barck et al. *(89)* showed that 500 μg/m^3 (0.27 ppm) nitrogen dioxide for 30 minutes enhanced the subsequent allergen-induced inflammatory reaction in the bronchi, as demonstrated by enhanced number of recruited neutrophils in the bronchial wash (BW) and BAL and levels of eosinophil granule product and eosinophil cationic protein in BW. To mimic real-life conditions, in which exposure to high ambient levels of nitrogen dioxide occurs only during short periods of time but often several times a day, these workers subsequently used a repeated-exposure model *(90)*. People with allergic asthma exposed on day 1 to 500 μg/m^3 (0.27 ppm) nitrogen dioxide for 15 minutes and on day 2 for two 15-minute intervals showed increased levels of eosinophil cationic protein in both blood and sputum post-allergen, although this was not accompanied by raised levels of neutrophils in sputum and blood.

In another recent study, 20 subjects were exposed in a road tunnel to a median nitrogen dioxide level of 313 g/m^3 (0.17 ppm) (range 203–462 μg/m^3; 0.11–0.25 ppm) for 30 minutes to study the effects of air pollution from traffic on allergic asthma *(77)*. Four hours later the subjects inhaled an allergen dose and the asthmatic reaction was measured. Subjects exposed to "tunnel nitrogen dioxide levels" ≥300 μg/m^3 (≥0.16 ppm) had a significantly greater early asthmatic reaction following allergen exposure, as well as lower lung function and more asthma symptoms during the late-phase asthmatic response, compared to controls. However, while representing a "real life" exposure, it should be noted that these effects occurred in the presence of 100 μg/m^3 $PM_{2.5}$, as well as possibly other pollutants such as volatile organic compounds and carbon monoxide.

Airway inflammation

Bronchoscopy with BAL collection and analysis after controlled chamber exposures has produced the opportunity to assess the airway effects of nitrogen dioxide in humans. Effects of nitrogen dioxide at high levels (5640–7520 μg/m^3; 3.0–4.0 ppm) on BAL cells and inflammatory mediators include a reduction in alpha-1-protease inhibitor activity *(1)*, increased numbers of neutrophils in healthy subjects exposed to 3760 μg/m^3 (2.0 ppm) for four or six hours with intermittent exercise *(100,101)* and decreased numbers of mast cells, certain classes of lymphocytes and alveolar macrophages (with increased phagocytic activity) in healthy subjects exposed to 7520 μg/m^3 (4.0 ppm) with intermittent exercise for 20 minutes a day, every other day for 12 days *(102)*. At lower concentrations of 1130 μg/m^3 (0.60 ppm), four separate two-hour exposures over six days resulted in no such responses *(103)*. Jörres et al. reported increased levels of thromboxane B2 and prostaglandin D2 in BAL fluid when individuals with mild asthma were

subjected to nitrogen dioxide (1880 μg/m^3; 1.0 ppm) for three hours during intermittent exercise (*104*).

Increases in the BAL inflammatory cell response (increased neutrophils and IL-8) in healthy subjects have been demonstrated, but only after exposure to nitrogen dioxide concentrations far in excess of those achieved in outdoor air (3600–6580 μg/m^3; 1.91–3.50 ppm) *(105,106)*. Utilizing lower levels of nitrogen dioxide, Frampton et al. *(107)* showed significantly increased levels of the antiprotease α2-macroglobulin 3½ hours after a 3-hour exposure to 1128 μg/m^3 (0.60 ppm).

The dose response and kinetics of nitrogen-dioxide-induced airway inflammation have been investigated in non-smoking healthy people. Concentration-dependent increases in mast cells and lymphocytes were found in BAL fluid after a single exposure to the occupational levels 3000–9000 μg/m^3 (1.60–4.79 ppm) nitrogen dioxide, with airway inflammation resolving within 72 hours of exposure *(108,109)*. Bronchoscopy with BAL has also been used to examine the kinetics of nitrogen-dioxide-induced antioxidant reactions. Exposure of healthy subjects to 3600 μg/m^3 (1.92 ppm) nitrogen dioxide results in rapid losses of ascorbate and uric acid, with concentrations returning to baseline levels at 6 and 24 hours, respectively. In contrast, glutathione concentrations increased at both 1½ and 6 hours after exposure to nitrogen dioxide but subsequently returned to control levels by 24 hours (*110*), suggesting only a temporary protective response.

The BAL inflammatory cell response in humans induced by repeated exposure to nitrogen dioxide has also been examined. Exposing healthy volunteers to 108 μg/m^3 (0.06 ppm) nitrogen dioxide for two hours on four separate days brought about a slight, but significant, increase in the percentage of natural killer lymphocytes *(71)*. In contrast, repeated exposure to 2820 and 7520 μg/m^3 (1.5 and 4.0 ppm) nitrogen dioxide for 20 minutes every second day for six days reduced B-cells and natural killer lymphocytes and altered the CD4+ : CD8+ cell ratio *(72,98)*. The effects of repeated exposure to nitrogen dioxide on inflammatory cell response, mediator levels, lung function and airway antioxidant status were examined in healthy subjects exposed to 3600 μg/m^3 (1.92 ppm) for four hours on four consecutive days. This sequential exposure resulted in a neutrophilic airway inflammation and depletion of antioxidants in the absence of persistent changes in pulmonary function *(111)*. Further sample analysis, to help elucidate the mechanism contributing to this acute inflammatory response, revealed upregulation in the expression of IL-5, IL-10, IL-13 and ICAM-1 (*112*). Upregulation of the Th2 cytokines suggests that repeated exposure to nitrogen dioxide has the potential to exert a "pro-allergic" effect on the bronchial epithelium, while upregulation of ICAM-1 provides a plausible mechanism for neutrophil influx during the acute inflammatory response and predisposition of respiratory tract virus infections following repeated exposure to nitrogen dioxide.

Host defences

Goings et al. *(113)* evaluated the effects of nitrogen dioxide on anti-viral defences. Healthy subjects were exposed to 1880–5600 μg/m^3 (1–3 ppm) for two hours per day for three days and then to an attenuated influenza virus. There was a non-significant trend for increased infectivity, but the results were inconclusive because the study had insufficient power to detect small differences in infectivity owing to the small number of subjects studied. Decreased inactivation of the influenza virus by alveolar macrophages has been demonstrated 3½ hours after a 3-hour nitrogen dioxide exposure to 1128 μg/m^3 (0.60 ppm) *(114)*.

Interaction of nitrogen dioxide with other air pollutants

Increased airway responsiveness to metacholine has been reported in healthy subjects who were first exposed to nitrogen dioxide (1130 μg/m^3; 0.6 ppm) and then to ozone *(115)*. In mild asthmatics, nitrogen dioxide at a concentration of 720 μg/m^3 (0.38 ppm) in combination with sulfur dioxide at 7000 μg/m^3 enhanced the airways response to inhaled allergen that reached a maximum 24 hours after exposure and remained until at least the following day *(116,117)*. This exposure protocol makes it difficult to assess the nitrogen dioxide effect with precision, but the principle of the persistence of response is important.

Exposure to diesel engine exhaust at 100 or 300 μg/m^3 PM_{10}, with nitrogen dioxide concentrations of 1000 and 2700 μg/m^3 (0.53 and 1.44 ppm), respectively, resulted in an inflammatory responses that included neutrophil, mast cell and lymphocyte infiltration of the airways, together with enhanced adhesion molecule expression in the bronchial mucosa and activation of the bronchial epithelium to produce a multitude of inflammatory cytokines *(118,119)*. Notably, none of these effects was seen after a single or repeated exposure to nitrogen dioxide at doses some 8–40 times greater than these *(106,111)*. An additive or synergistic effect of nitrogen dioxide in the diesel engine exhaust is possible, but in this setting the development of inflammation is unlikely to be driven by nitrogen dioxide. Support for this conclusion is provided by Nightingale et al., who exposed healthy volunteers for two hours to resuspended (i.e. old) diesel particles with 200 μg/m^3 PM_{10} and found changes in exhaled carbon monoxide and sputum neutrophils and myeloperoxidase six hours post-exposure *(120)*.

The respiratory impact of two-hour combinations of inhaled PM (predominantly in the fine ($PM_{2.5}$) size range, at concentrations near 200 μg/m^3) and nitrogen dioxide (752 μg/m^3; 0.4 ppm) has also been studied in elderly people with and without COPD *(97)*. Respiratory symptoms, spirometry, and total and differential counts of induced sputum cells showed no statistically significant responses attributable to separate or combined effects of fine particles and nitrogen dioxide. Exposure to fine particles alone was, however, associated with small but statistically significant decrements in maximum mid-expiratory flow and arterial oxygen and with lower percentages of columnar epithelial cells in the sputum.

These results indicate that the respiratory effect of the PM–nitrogen dioxide mixture may be primarily PM-driven, since co-exposure to nitrogen dioxide did not significantly enhance the responses.

Epidemiological studies

Epidemiological studies on the health effects of exposure to nitrogen dioxide have been extensively reviewed by WHO. The second edition of *Air quality guidelines for Europe* summarized the effects of several air pollutants, including nitrogen dioxide *(121)*. A 1-hour guideline of 200 μg/m^3 and an annual mean of 40 μg/m^3 were recommended. In 2003, to support the development of European Union policy on clean air for Europe (CAFE), a WHO Working Group reviewed the most recent scientific evidence on the adverse health effects of PM, ozone and nitrogen dioxide *(122)*. The review focused on studies that were published after the formulation of the second edition of the WHO guidelines. Finally, in 2004 the bases for the air quality guideline value for nitrogen dioxide were scrutinized *(123)*. Studies on the effects of air pollutants on children's health, including nitrogen dioxide, were reviewed in a WHO monograph *(124)*. Epidemiological studies that have considered outdoor and indoor exposures to nitrogen dioxide will be reviewed here, with special emphasis on studies conducted in the last decade.

From the point of view of epidemiological studies, there are important characteristics of nitrogen dioxide that should be noted. Nitrogen dioxide is strongly related to PM, as both come from the same combustion sources, and it is converted to nitrates and contributes per se to fine particle mass. Several studies have noted a high correlation between nitrogen dioxide levels and suspended PM generated from the same combustion sources. At a given site, a high correlation exists between nitrogen dioxide and organic and elemental carbon, inorganic acids, $PM_{2.5}$ and ultrafine particles *(125–128)* so that nitrogen dioxide may be considered a very good indicator of the complex gas–particle mixture that originates from vehicular traffic.

Thus it is very difficult to differentiate the effects of nitrogen dioxide from those of other pollutants in epidemiological studies. As a result, outdoor studies are more informative when (*a*) the temporal or spatial distributions of nitrogen dioxide or PM (PM_{10}, $PM_{2.5}$ or black smoke (BS)) are different (e.g. they compare time periods or areas that rank differently in nitrogen dioxide and PM, respectively) and (*b*) this (partial) independence is used to evaluate the nitrogen dioxide effect controlling for the effect of PM, or alternatively to show that high nitrogen dioxide levels enhance the risk of PM. The latter may be because nitrogen dioxide per se enhances the effect of PM, or that high nitrogen dioxide levels indicate the presence of more noxious components of PM *(122)*. Finally, short-term studies are usually based on day-to-day variability in the pollutants at a few central monitors. PM (especially $PM_{2.5}$) concentrations are rather homogenous in large areas and day-to-day variability in population exposure is well-represented by

Table 2. Selected outdoor population-based studies on short-term adverse health effects of nitrogen dioxide

Reference	Location	Type of study	Outcome	PM levels
Stieb, Judek & Burnett *(129)*	32 locations worldwide	Meta-analysis of time series studies	Daily mortality	PM_{10}, range of means 26.9–123.2 μg/m^3
Anderson et al. *(130)*	London, United Kingdom	Time series of hospital admissions	Asthma admissions (0–14 years)	BS, mean 14.6 (SD 7.0) μg/m^3
Hajat et al. *(131)*	London, United Kingdom	Time series of family doctor consultations	Asthma in children	PM_{10}, mean 28.5 (SD 13.7) μg/m^3
Lin et al. *(132,133)*	Toronto, Canada	Case-crossover of hospital admissions	Asthma in children (6–12 years)	PM_{10}, mean 30.1 (SD 13.6) μg/m^3
Metzger et al. *(134)*	Atlanta, USA	Time series of visits to emergency departments (1993–2000)	All cardiovascular Ischaemic heart disease	PM_{10}, median 23.3 μg/m^3 (10%–90%, 13.2–44.7)
Barnett et al. *(135)*	Seven cities in Australia and New Zealand	Case-crossover of hospital admissions	All respiratory (5–14 years) Asthma (5–14 years)	PM_{10} , range of means 16.5–20.6 μg/m^3
Peel et al. *(136)*	Atlanta, USA	Time series of visits to emergency departments (1993–2000)	All respiratory COPD Asthma Paediatric asthma	PM_{10}, mean 27.9 (SD 12.3) μg/m^3

PM effects	PM–nitrogen dioxide correlation	Nitrogen dioxide levels	Nitrogen dioxide effects	PM-adjusted nitrogen dioxide effects
2.0% (CI 0.4–2.1) per 31.3 μg/m^3	NA	Range of means 20.4–103.3 μg/m^3	2.8% (CI 2.1–3.5) per 24 ppb	0.9% (CI –0.1–2.0) in multi-pollutant model
0.58% (CI –1.27–2.46) per 10 μg/m^3	NA	Mean 37.2 (SD 13.2) pbb	1.25% (CI 0.3–2.2) per 10 pbb	2.26% (CI 0.83–3.71) per 10 pbb, adjusting for BS
3.8% (CI –1.0– 8.8) per 16.5 μg/m^3	0.73	Mean 33.6 (SD10.5) pbb	6.1% (CI 1.2–11.3) per 22.5 pbb	No two-pollutant model needed as PM_{10} not significant in single-pollutant model
14% increase (CI 2–28) in boys and 18% (CI 0.2–36) in girls per 8.4 μg/m^3 $PM_{10–2.5}$ (coarse particles)	0.52	Mean 25.2 (SD 9.0) pbb	NA	12% increase (CI 1–23) in boys and 16% (CI 2–31) in girls per 11 ppb increase in nitrogen dioxide, adjusting for $PM_{2.5}$ and PM_{10}
0.9% (CI –0.2–1.9) per μg/m^3	0.49 (1 hour)	Median (1 hour) 44.0 pbb	2.5% (CI 1.2–3.9) per 20 pbb 1-hour nitrogen dioxide	No two-pollutant model needed as PM_{10} not significant in single-pollutant model
1.1% (CI –0.8–3.0) per 10 μg/m^3		(10%–90%, 25–68)	2.9% (CI 0.5–5.3) per 20 pbb	
1.9% (CI 0.1–3.8) per 7.5 μg/m^3	0.25–0.57	Range of means 7.0–11.7 pbb	5.8% (CI 1.7–10.1) per 5.1 pbb	6.4% (CI 3.0–9.8) and PM_{10} no longer significant
1.7% (CI –1.7, 5.3) per 7.5 μg/m^3			6% (CI 0.2–12.1) per 5.1 pbb	No two-pollutant model needed as PM_{10} not significant in single-pollutant model
1.3% (CI 0.4–2.1) per 10 μg/m^3	0.49 (1 hour)	Mean (1 hour) 45.9 (SD17.3) pbb	1.6% (CI 0.6–2.7) per 20 pbb 1-hour nitrogen dioxide	Nitrogen dioxide effect for asthma not attenuated, while the estimates for other pollutants suggested weaker or no association
1.8% (CI –6.0–4.3) per 10 μg/m^3			3.5% (CI 0.6–6.5) per 20 pbb 1-hour nitrogen dioxide	
9.9% (CI 6.5–13.5) per 10 μg/m^3			4.7% (CI 1.1–8.5) per 20 pbb 1-hour nitrogen dioxide	
1.6% (CI –0.2–3.4) per 10 μg/m^3			2.7% (CI 0.5–5.0) per 20 pbb 1-hour nitrogen dioxide	

the few monitors. On the other hand, a greater spatial variability exists for nitrogen dioxide, and it is therefore likely that daily variation in exposure to nitrogen dioxide is less well-described than in the case of PM, resulting in a greater possibility of misclassification.

Outdoor population-based studies: short-term effects

A large number of time series studies have used maximum hourly concentrations and/or daily mean concentrations of nitrogen dioxide to evaluate a wide range of short-term adverse health effects. The studies have been conducted at the population level, including large cities in the world, or among subjects with pre-existing chronic diseases such as asthmatics. Table 2 lists the results of selected studies on short-term effects of nitrogen dioxide.

Time series studies on mortality

A meta-analysis of time series investigations on daily mortality, which incorporated 109 studies published between 1982 and 2000, with data from 1958–1999 *(129)*, included 32 effect estimates for nitrogen dioxide from single-pollutant models and 15 from multi-pollutant models. Over a 24-hour range of mean nitrogen dioxide exposure (20.4–103.3 μg/m^3), the overall effect estimate from the single-pollutant model for all-cause mortality was 2.8% (95% CI 2.1–3.5) per 24 ppb nitrogen dioxide (24-hour), which fell to 0.9% (95% CI –0.1–2.0) in multi-pollutant models, including particles. In single-pollutant models, the effect estimate for nitrogen dioxide on respiratory deaths was higher (6.6 ± 1.6%), whereas for cardiovascular deaths (3.2 ± 0.5%) it was similar to the value derived for all-cause mortality. The conclusion of the meta-analysis did not change when the methodological issues related to the use of generalized additive models (GAM) for the data analysis were considered *(137)*.

The results of multi-city studies conducted in Europe should be mentioned, because the effect of nitrogen dioxide has been careful evaluated. The European APHEA 1 study – the first European initiative on short-term health effects of air pollution *(138)* – found a statistically significant effect of nitrogen dioxide on daily mortality: a 1.3% increase in daily deaths (95% CI 0.9–1.8) per 50 μg/m^3 nitrogen dioxide (1-hour maximum) *(139)*. The effect remained statistically significant (0.6%, 95% CI 0–1.2) after adjusting for BS. The APHEA 2 study on daily mortality in 29 cities *(140)* found that PM effects on daily mortality were stronger in areas with high nitrogen dioxide levels. The overall estimated increase in the daily number of deaths for all ages for a 10-μg/m^3 increase in daily PM_{10} was 0.6% (95% CI 0.4–0.8); in cities with low average nitrogen dioxide, however, the estimated increase in daily mortality for the same-sized increase in PM_{10} was 0.19 (95% CI 0.00–0.41), whereas in a city with high average nitrogen dioxide it was 0.80% (95% CI 0.67–0.93). Finally, the APHEA 2 study reported, for nine European cities, an increase of 2% in natural all-cause mortality per 50 μg/m^3 nitrogen

dioxide in the daily maximum 1-hour value, with a near-linear dose–response function in the range between 100 μg/m^3 and 200 μg/m^3 *(141)*.

The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) analysed the association between daily air pollution and daily deaths in 90 United States cities for the period 1987–1994. NMMAPS found a positive association between PM_{10} and daily mortality *(142,143)*. The relative increase in daily mortality was 0.21% (SE 0.06%) per 10-μg/m^3 increase in PM_{10} concentration one day prior to the event. The presence of other pollutants in the model did not change this effect. Nitrogen dioxide showed statistically significant relative increases in daily mortality from 0.3% to about 0.4% per 10 ppb (previous day concentration, lag 1). This effect remained but lost statistical significance after adjusting for PM_{10} and ozone.

In summary, daily concentrations of nitrogen dioxide are significantly associated with increased overall, cardiovascular and respiratory mortality. The effect estimate for overall mortality derived from a well-conducted meta-analysis is a 2.8% increase per 24 ppb. Adjusting for the effect of PM reduces the effect estimate to 0.9%, and the lower confidence interval of the effect estimate includes zero *(129)*. In the European cities studied *(140,141)*, the effect of PM on daily mortality was greater in areas with high nitrogen dioxide levels.

Time series studies on morbidity among adults

There have been several time series studies published on the effects of nitrogen dioxide on daily hospital admissions for respiratory disorders. Three quantitative summaries of the APHEA 1 city-specific results evaluated the relationship between various pollutants (particles and gases) and (*a*) total hospital admissions for respiratory problems in five cities *(144)*; (*b*) hospital admissions for COPD in six cities *(145)*; and (*c*) emergency admissions for asthma in four cities *(146)*. Nitrogen dioxide was associated with COPD but not with total respiratory conditions, but a BS effect was detected only in the presence of high nitrogen dioxide levels, a finding in keeping with APHEA 2 results on daily mortality. The results for asthma were less consistent since positive associations with nitrogen dioxide were found, though not in all age groups and not in all cities *(130,146)*. In the study by Anderson et al. *(130)*, the effect of nitrogen dioxide on asthma admissions in London remained unchanged after adjusting for BS, ozone and pollen. More recently, Galàn et al. *(147)* did find that the effect of nitrogen dioxide on asthma admissions in Madrid was independent of the effects of other pollutants (not PM_{10}) and pollen exposure. The adjusted effect estimate in this study was 2.4% (95% CI 0.5–4.5) per 10 μg/m^3, similar to that estimated for London *(130)*. Adjusting for PM_{10}, however, attenuated the effect estimate for nitrogen dioxide towards the null, given the high correlation of the two pollutants.

The association between air pollutants and emergency department visits for respiratory problems in Atlanta, Georgia, was evaluated in a study published in

2005 *(136)*. Daily measurements of five pollutants (PM_{10}, ozone, nitrogen dioxide, carbon monoxide and sulfur dioxide) were available from January 1993 to August 2000. The mean daily 1-hour maximum nitrogen dioxide value was 45.9 ppb. Detailed measurements of PM were available for 24 months. Visits for asthma, COPD, upper respiratory infections and pneumonia were evaluated. Considering an a priori three-day lag (lag 0–2), PM_{10}, ozone, nitrogen dioxide and carbon monoxide were associated with all respiratory admissions and with upper respiratory infections. The effect for 20 ppb 1-hour nitrogen dioxide was 1.6% (95% CI 0.6–2.7) for all respiratory conditions and 1.9% (95% CI 0.6–3.1) for upper respiratory infections. Visits for COPD were associated only with 1-hour nitrogen dioxide (3.5% per 20 ppb, 95% CI 0.6–6.5) and carbon monoxide. For asthma, a stronger effect was detected considering distributed lag models (lags 0–13 days), with PM_{10}, nitrogen dioxide (4.7% for 20 ppb, 95% CI 1.1–8.5) and carbon monoxide showing a statistically significant effect. Paediatric asthma visits (ages 2–18 years) showed a strong association only with nitrogen dioxide (2.7% per 20 ppb, 95% CI 0.5–5.0). In multi-pollutant models, the nitrogen dioxide effects were attenuated when PM_{10}, nitrogen dioxide and carbon monoxide were considered simultaneously. However, the effect of nitrogen dioxide on emergency visits for asthma was not attenuated in multi-pollutant models, while the estimates for the other pollutants suggested a weak association or none at all.

Observations are also available on nitrogen dioxide and hospital admissions for cardiovascular diseases. In the studies by Polonieski et al. *(148)* (myocardial infarction), Burnett et al. *(149)* (all cardiovascular admissions), Burnett et al. *(150)* (ischaemic heart disease, heart failure), Atkinson et al. *(151)* (all cardiovascular), Wong e al. *(152)* (all cardiovascular, heart failure) and D'Ippoliti et al. *(153)* (myocardial infarction), a statistically significant effect was found for nitrogen dioxide. In some of these studies, the effect estimates were moderated and sometimes became non-significant when the investigators controlled for particle concentrations. In the studies by Schwartz *(154)* (all cardiovascular) and Morris et al. *(155)* (heart failure), no effect of nitrogen dioxide was found.

Two recent large American studies evaluated nitrogen dioxide and other pollutants and their relationship with hospital admissions for ischemic heart disease *(156)* and visits to emergency departments for cardiovascular problems *(134)*. Mann et al. *(156)* examined whether admissions for ischemic heart disease were associated with air pollutants in subjects with and without secondary diagnoses of arrhythmia or congestive heart failure, using a large data set of members of a large health maintenance organization who resided in the South Coast Air Basin of California from 1988 to 1995. Daily variations in carbon monoxide, nitrogen dioxide, ozone and PM_{10} were considered. Carbon monoxide and nitrogen dioxide (mean 37.2 ppb, interquartile range 3.7–138) were both associated with admissions, with the greatest effects for carbon monoxide. PM_{10} was not associated with hospital admissions in this study but particle concentrations were available

only every six days. A 10-ppb increase in 24-hour average nitrogen dioxide was associated with a 2.32% (95% CI 0.69–3.98) increase in same-day admissions for ischemic heart disease in persons with a secondary diagnosis of congestive heart failure, a 1.81% (0.78–2.85%) increase in persons with a secondary diagnosis of arrhythmia, and a 1.30% (95% CI 0.51–2.10) increase in ischemic heart disease admissions in persons without either secondary diagnosis. Carbon monoxide and nitrogen dioxide were not evaluated in multi-pollutant models because of the collinearity of the two. Air pollution was most strongly associated with hospital admissions for myocardial infarction. This study suggests that people with ischemic heart disease and accompanying congestive heart failure and/or arrhythmia constitute a subgroup particularly sensitive to the effects of ambient air pollutants associated with internal combustion engines.

Metzger et al. *(134)* examined the relationship between ambient air pollution and cardiovascular conditions using ambient air quality data and emergency department visit data in Atlanta, Georgia (1993–2000). Data on 4 407 535 emergency department visits were collected, as well as measurements of air pollutants for the entire study period. Moreover, detailed measurements were taken of mass concentrations for fine and coarse fractions of PM and several physical and chemical characteristics of PM for the final 25 months of the study. The median of 1-hour maximum level of nitrogen dioxide during the study period was 44 ppb (10–90%, range 25.0–68.0). Using an a priori three-day moving average in single-pollutant models, cardiovascular visits were associated with nitrogen dioxide, carbon monoxide, $PM_{2.5}$, organic carbon, elemental carbon and oxygenated hydrocarbons. However, the effects tended to be strongest with same-day pollution levels. The effect estimate for 20 ppb 1-hour nitrogen dioxide (three-day average) on all cardiovascular emergency department visits was 2.5% (95% CI 1.2–3.9). Carbon monoxide had a strong effect in this study (correlation coefficient between carbon monoxide and nitrogen dioxide = 0.68), whereas PM_{10} did not have a significant effect. Adjusting for carbon monoxide in the bi-pollutant model reduced the effect estimate for nitrogen dioxide, but it remained statistically significant. When adjusting for $PM_{2.5}$ for the shorter period of data availability (two years), the nitrogen dioxide effect was not statistically significant. Emergency department visits for ischemic heart disease were associated only with nitrogen dioxide for the entire period of the investigation (2.9% (95% CI 0.5–5.3) for 20 ppb 1-hour nitrogen dioxide), while for the shorter period the effect of oxygenated hydrocarbon was statistically significant.

Wellenius et al. *(157)* evaluated the association between air pollutants and hospital admission rate for congestive heart failure among Medicare recipients (65+ years) in Allegheny County, Pennsylvania, during 1987–1999. The daily mean level of nitrogen dioxide was 26.5 ppb and this pollutant was highly correlated with PM_{10} (0.64) and carbon monoxide (0.70). The strongest effects were found for nitrogen dioxide (4.2% per 11 ppb 24-hour nitrogen dioxide, 95% CI 2.6–5.8)

and carbon monoxide and they were robust in two-pollutant models adjusting for PM_{10}. When nitrogen dioxide was adjusted for carbon monoxide, the nitrogen dioxide effect was null.

Finally, Peters et al. *(158)* suggested a role for air pollution on heart rhythm disorders among patients with implanted defibrillators in a study conducted in the Boston area. In this study, $PM_{2.5}$, BS, nitrogen dioxide and carbon monoxide were associated with increased risk of defibrillator discharges, and the concentration–response relationship for nitrogen dioxide was the steepest. In a new study published in 2005, the association between air pollution and severe arrhythmia among patients with implantable cardioverter defibrillators was again evaluated in Boston *(159)*. A total of 798 ventricular arrhythmias among 84 subjects were analysed using a case-crossover design. Hourly and daily levels of $PM_{2.5}$, black carbon, nitrogen dioxide, sulfur dioxide, carbon monoxide and ozone were available. The median daily nitrogen dioxide concentration was 22.4 ppb. $PM_{2.5}$ and ozone from the previous 24 hours were associated with arrhythmia, while similar effects for nitrogen dioxide and sulfur dioxide were detected but for the previous 48-hour moving averages. For nitrogen dioxide, an interquartile range of 7.7 ppb over the last 48 hours increased the probability of severe arrhythmia by 18% (95% CI 4–35). In two-pollutant models (where the nitrogen dioxide in the previous 24 hours was considered), the effect of nitrogen dioxide was not independent of the effect of $PM_{2.5}$, whereas controlling for ozone did not attenuate the nitrogen dioxide effect.

In summary, the results of time series studies on nitrogen dioxide and hospital admissions/emergency department visits for respiratory and cardiovascular diseases seem to indicate a nitrogen dioxide effect. Controlling for other pollutants at times lowers the effect estimates and at others makes them not statistically significant, and this makes the conclusions less clear. In some studies, however, especially those on asthma admissions, nitrogen dioxide rather than PM was associated with health effects. The results of recent studies conducted in the United States on emergency department visits for respiratory *(136)* and cardiovascular disorders *(134)* provide the basis for health risk evaluation.

Time series studies on asthma morbidity among children

Time series analysis has been used to report associations between daily air pollutants and hospital admissions or emergency department visits for asthma in children.

European time series analyses (conducted mostly within the APHEA 1 initiative) have suggested that gaseous air pollutants, as well as particulate mass, are important determinants of acute hospital admission for respiratory conditions. As indicated above, three quantitative summaries of the APHEA city-specific results have evaluated the relationship between various pollutants (particles measured as either BS or total suspended particulates, sulfur dioxide, nitrogen dioxide

and ozone) and total respiratory hospital admissions in five cities *(144)*, admissions for COPD in six cities *(145)* and emergency admissions for asthma in four cities *(146)*. The study by Sunyer et al. *(146)* considered three cities (Helsinki, London and Paris) with data available on children aged 0–14 years during the period 1987–1992; London and Paris contributed the most, since the number of asthma admissions in Helsinki was limited. The strongest and most statistically significant effect was found for nitrogen dioxide, with an estimated increase of 3.7% (0.4–6.7%) per 50 μg/m^3 at a cumulative lag of three days. BS was also associated with asthma admissions (4.6% per 50 μg/m^3) but the estimate was not statistically significant. No effect was found for ozone (0.6% per 50 μg/m^3). Sulfur dioxide was also related to hospital admissions for children's asthma in this study.

More recent investigations, following the APHEA 1 results, have analysed hospital admissions or emergency department visits for asthma, particularly in children. The series of observations in London are of importance. The 1987–1992 data set in London has been analysed by Anderson et al. *(130)*, considering the possibility of confounding/interacting effects of aeroallergens. In a single-pollutant model, only nitrogen dioxide and sulfur dioxide were significantly related to children's hospital admissions. Associations with BS and ozone were lower and statistically not significant. Atkinson et al. *(160)* analysed hospital admissions for asthma during 1992–1994 in London, and for the first time in a European study considered PM_{10} together with other pollutants. All pollutants except ozone were associated positively with asthma admissions, although none of the associations was statistically significant. Analysis of the association between outdoor pollutants and visits to emergency departments for respiratory complaints in London during 1992–1994 *(151)* revealed a strong relationship between nitrogen dioxide levels and asthma visits in children, especially during the warm season. PM_{10} and BS also had an effect. A parallel analysis of daily consultations by general practitioners for asthma and other lower respiratory conditions in London showed strong effects for nitrogen dioxide in children, again particularly during summer, whereas no effect was found in adults *(131)*.

The results found in the time series analysis of respiratory admissions in Rome during 1995–1997 were very similar to what has been suggested by the London studies with regard to children's asthma admissions: nitrogen dioxide was strongly related to total respiratory admissions, and in particular to acute respiratory infections and asthma among children *(161)*. No statistically significant effect of PM was found in this investigation.

The results of the APHEA 2 study evaluating the association between PM and respiratory hospital admissions in eight cities were published in 2001 *(162)*. The paper considered PM_{10} and BS as the main factors of interest, whereas gaseous pollutants were considered only to evaluate their potential confounding role. The summary estimates a 1.2% increase in PM_{10} and a 1.3% increase in BS for each

10 μg/m^3. In multi-pollutant models, ozone and sulfur dioxide did not substantially alter the effect estimates for PM_{10} and BS, but including nitrogen dioxide in the models dramatically reduced the PM_{10}/BS effect. Such confounding from nitrogen dioxide has been interpreted to indicate that the particles' effects may be due to being derived from traffic-related sources, and strongly correlated with nitrogen dioxide.

Anderson et al. *(163)* evaluated a range of air pollutant measures, considering hospital admissions in the West Midlands conurbation in England from 1994 to 1996. Separate measures for fine ($PM_{2.5}$) and coarse ($PM_{10–2.5}$) particles were available in this study, together with PM_{10}, BS and gases. Strong and statistically significant effects for PM_{10} and BS (and sulfur dioxide) were found, but neither $PM_{2.5}$ nor $PM_{10–2.5}$ was better than PM_{10} at predicting asthma hospital admissions. The effect of nitrogen dioxide was borderline significant.

Emergency department visits in Seattle for childhood asthma during 15 months in 1995/1996 were evaluated in relation to PM, nitrogen dioxide and other pollutants *(164)*. A nephelometer was used to measure fine particles, by measuring the coefficient of light scattering by particles approximately equal to $PM_{1.0}$ or below 1 μm in diameter. The study found small but statistically significant effects of PM_{10} and fine particles. One-hour maximum nitrogen dioxide also had an effect, although it was not significant.

A report from Sydney, Australia, indicated 1-hour maximum nitrogen dioxide as the single most relevant pollutant related to admissions for childhood asthma *(165)*. Daily hospital admissions during 1990–1994 were considered in this study, which used a nephelometer to measure nitrogen dioxide, ozone and particulates. While the effect of nitrogen dioxide was large and robust in sensitivity analyses, both ozone and particulates had a (non-significant) protective effect. In the analysis of hospital admissions data in Brisbane during 1987–1994 *(166)*, the only pollutant associated with asthma admissions in the 0–14-year age group was ozone. Particles (as measured by nephelometer) and nitrogen dioxide had non-significant protective effects.

Only one report is available from Asia. Lee et al. *(167)* analysed hospital admissions for acute asthma in Seoul, Republic of Korea, during a two-year period. PM_{10}, nitrogen dioxide and ozone were all related to asthma admissions, the strongest and most robust effects being for nitrogen dioxide and ozone.

A comprehensive study was conducted in Canada that specifically evaluated the role of fine and coarse particles and gaseous pollutants *(132,133)*. A total of 7319 hospital admissions for asthma in children 6–12 years of age (4629 for boys and 2690 for girls) in Toronto between 1981 and 1993 were considered *(133)*. The annual average nitrogen dioxide concentration was 25.2 ppb (interquartile range 19–30 ppb). Estimates were calculated for one- to seven-day average levels of each gaseous pollutant. Nitrogen dioxide was positively associated with hospital admission for asthma in both boys and girls. However, the lag time for the

nitrogen dioxide effect seemed to be different in boys and girls. In boys, nitrogen dioxide showed no significant effect until three days of accumulated exposure, and seemed to increase slightly with number of days of exposure up to an average of six days. In girls, only seven-day exposure averages consistently showed a significant effect on asthma hospital admissions. The effect estimates at six-day cumulative lag were increases of 12% (1–23%) in boys and 16% (2–31%) in girls per 11 ppb increase in nitrogen dioxide. The effect for nitrogen dioxide did not change after adjusting for coarse PM.

Daily air pollution levels and daily respiratory hospital admissions in children (three age groups: 0, 1–4 and 5–14 years) for five cities in Australia and two cities in New Zealand were analysed using city-specific case-crossover methods and pooling the results with meta-analysis *(135)*. Levels of air pollution in these countries were generally lower than in other locations studied in Europe and the United States. All respiratory admissions, asthma, and pneumonia plus acute bronchitis were considered. The mean 24-hour nitrogen dioxide concentration ranged from 7.0 ppb to 11.7 ppb and the nitrogen dioxide–$PM_{2.5}$ correlation was from 0.34 to 0.68. In the 1–4-year age group, both $PM_{2.5}$ and nitrogen dioxide were associated with total respiratory admissions, the largest effect found being for nitrogen dioxide (2.8% increase per 9.0 ppb 1-hour nitrogen dioxide, 95% CI 0.7–4.9); in 5–14-year-olds, an association was found with PM_{10} and nitrogen dioxide, again with the strongest effect for nitrogen dioxide (5.8% per 5.1 ppb 24-hour nitrogen dioxide, 95% CI 1.7–10.1). In general, the largest association found was a 6% (95% CI 0.2–12.1) increase in asthma admissions related to an interquartile range (5.1 ppb) increase in 24-hour nitrogen dioxide. A matching technique (control days) was used to evaluate the effect of a pollutant while controlling for the effect of another. In the 1–4-year age group, controlling for PM_{10} attenuated the effect of nitrogen dioxide to a non-significant value, whereas in the 5–14-year age group, controlling for PM_{10} did not affect the results for nitrogen dioxide while the effect of PM_{10} was sensitive to the effect of nitrogen dioxide. The impact of nitrogen dioxide was stronger in warmer cities and during the summer.

Finally, the study on emergency department visits in Atlanta *(136)* has been mentioned, giving a relative risk of 1.027 (95% CI 1.005–1.050) per 20-ppb increase in 1-hour nitrogen dioxide concentration for paediatric asthma (2–18 years).

In summary, a consistent association between air pollution and hospital admissions, emergency department visits and visits to the doctor for asthma in children has been found in epidemiological studies. Most of the studies indicated an effect of PM and ozone. In many of the recent studies, however, nitrogen dioxide was strongly related to hospital admissions or emergency department visits for asthma, and there are several instances when nitrogen dioxide was the only pollutant associated with health effects or where the effect remained after adjusting

for other pollutants. The large studies conducted in Canada *(133)*, Australia and New Zealand *(135)* and the United States *(136)* provide a basis for health risk evaluation.

Panel studies on asthmatic children

Panel studies among asthmatic children and children with chronic respiratory symptoms combine individuals with different degrees of asthma severity and medication use who record daily health outcomes over several months. Air pollution is measured concurrently with potential confounders that also change on a daily basis (e.g. weather factors, days of week). There are various outcomes, such as symptoms (cough, wheeze, shortness of breath with wheeze, asthma attacks), medication use (bronchodilator or ß-agonist) or lung function changes (e.g. peak expiratory flow (PEF), FEV_1 and FVC), requiring subjects to perform unsupervised daily PEF tests or to attend repeated supervised spirometry tests.

Panel studies of asthmatic children have been conducted in European countries. Children in urban and rural areas of the Netherlands were studied by Boezen et al. *(168)* and categorized according to their bronchial hyperresponsiveness and serum IgE. Based on data from three winters, there was a strong association between the occurrence of lower respiratory tract symptoms, including wheeze, and both PM_{10} and nitrogen dioxide among subjects with increased bronchial hyperresponsiveness and high serum IgE levels. Associations were found only among children who had both of these conditions. Evening PEF was also negatively influenced by PM_{10} and nitrogen dioxide. Van der Zee et al. *(169)* examined PEF and respiratory symptoms among children with and without asthma, chronic cough or wheeze (classified as symptomatic) in urban and rural areas. In the urban areas, associations were found between PM_{10} and lower respiratory symptoms, medication use and a decrease in PEF among the symptomatic children. The only effects of nitrogen dioxide were increased frequency of bronchodilator use. Only minimal effects were observed in the non-urban areas. No associations were found among the non-symptomatic children. Finally, the European study PEACE, conducted in 14 centres, evaluated 2010 symptomatic children with a follow up of two months. There was no clear association of PM_{10}, BS or nitrogen dioxide with various outcomes, including symptoms, medication use and PEF measurements. This study was conducted during the winter of 1993–1994, which had a particularly severe influenza epidemic *(170)*.

Two studies have been conducted in Paris, France. Segala et al. (*171*) studied 43 children with mild and 41 with moderate asthma for six months. Nocturnal cough was the symptom most strongly associated with air pollution in mild asthmatics, in particular PM_{13}, BS and nitrogen dioxide. No association between pollutants and PEF was found in the whole group, but restricting the analysis to 21 children who did not take corticosteroids and no regularly scheduled ß-agonist revealed borderline statistically significant effects for PM_{13} and nitrogen dioxide.

A later study *(172)* examined symptoms, medication use and PEF among 82 children over three months. Again, nocturnal cough was associated with BS and nitrogen dioxide, whereas no association was found for ozone.

Several studies on asthma aggravation have been conducted in the United States. One pilot study on 30 asthmatic children conducted by Quackenboss et al. *(173)* in Tucson, Arizona, suggested an association of PM_{10} and nitrogen dioxide with PEF, using both central monitors and personal measurements for two weeks. Delfino et al. *(174)* examined a panel of asthmatics living in a semi-rural area of Southern California that has high levels of summer smog. The panel of 24 asthmatics, 9–17 years old, were followed from August to October 1995. Asthma symptoms were associated with both PM_{10} and ozone, with a greater relative effect from PM_{10}. The largest effects of PM_{10} were on those children not currently on anti-inflammatory medication. In a later study conducted in the same location, Delfino et al. *(175)* confirmed the association of PM_{10} and ozone with asthma symptoms and found nitrogen dioxide also to be a relevant pollutant. Pollens were also adjusted for in this study. Effects were stronger in children with respiratory infections and in children who were not taking anti-inflammatory medication. The latest report from the same group *(176)* evaluated asthma symptoms among Hispanic children living in an area of Los Angeles County with major roads and freight routes. A total of 22 asthmatics were followed, and were provided with a diary to monitor symptoms. Significant associations were found for PM_{10} and nitrogen dioxide.

Results of the National Cooperative Inner-City Asthma Study (an investigation conducted in eight urban areas in the United States) were reported by Mortimer et al. *(177)*. A total of 846 children were followed for two weeks during the summer by means of a diary and PEF measurements. All the pollutants investigated (PM_{10}, nitrogen dioxide, ozone and sulfur dioxide) were related to increases in morning symptoms. Only ozone was related to a decline in morning PEF.

Finally, since episodes of airflow obstruction and aggravation of symptoms in asthmatic subjects are often precipitated by viral infections, the study of Linaker et al. *(178)* is relevant. They investigated 114 asthmatic children and followed them for 13 months for respiratory infection and development of asthmatic symptoms, and measured personal nitrogen dioxide exposure. The air pollutant was strongly associated with the risk of asthmatic exacerbations following respiratory infections.

To summarize, the panel study results on effects of air pollution in children are rather inconsistent, mainly because the large PEACE study did not show an effect for any of the measured pollutants. The inconsistent results could be due to the difficulties in finding the appropriate panel in terms of size, length of follow-up, composition (with or without symptoms, asthma therapy, sensitization, severity), compliance, and intervening factors such as an influenza epidemic. Nevertheless, despite the overall inconsistency in panel study results, those with a large number

Table 3. Long-term effects of nitrogen dioxide: asthma, respiratory disorders and lung-function growth in selected cohort studies

Reference	Area, population, period	Outcome
Shima & Adachi *(179)*	7 communities in Japan with different levels of air pollution; pupils (n = 842) aged 9–10; annual questionnaire 1992–1994	Wheeze and asthma
Brauer et al. *(180)*	Prospective birth cohort (n = 3745), age 2 years, from a series of rural and urban communities in the Netherlands (1996–2001)	Asthma, respiratory symptoms up to 2 years of age
Gehring et al. *(181)*	Prospective birth cohort (n = 1757), living in Munich, Germany, follow-up until age 2 years (1996–2001)	Asthma, respiratory symptoms up to 2 years of age
Emenius et al. *(182)*	Nested case–control study, n = 540 (181 cases with recurring wheezing and 359 age-matched controls) based on a birth cohort from Sweden (n = 4089) (1994–1998)	Recurrent wheeze at age 2 years
McConnell et al. *(127)*	12 communities in Southern California with different levels of air pollution; pupils with asthma (n = 475) aged 9–13 years in 1993, with two or more follow-up questionnaires between 1996 and 1999	Bronchitic symptoms
Gauderman et al. *(183)*	12 communities in Southern California with different levels of air pollution; 1759 fourth-graders enrolled in 1993 aged 9–11 years (1993–2001)	Growth rate of lung function (FVC, FEV_1, maximum mid-expiratory flow (MMEF))

of children-days indicate an effect of nitrogen dioxide on symptoms and infection defence mechanisms. The results are in keeping with the findings of asthma hospital admissions and indoor studies (see below), showing a clear effect of nitrogen dioxide on the incidence of viral infections among asthmatics.

Nitrogen dioxide unit (mean)	Nitrogen dioxide odds ratio (95% CI)	Comments
10 ppb (range of 3-year average 7.0–31.3 ppb)	1.76 (1.04–3.23) wheeze, adjusted 2.10 (1.10–4.75) asthma, adjusted	Incidence of asthma (range 0–3.6%) and wheeze (range 0–6.5%) was low; no absolute numbers are given.
10.3 μg/m^3 (range of annual averages 12–58 μg/m^3)	1.13 (0.99–1.29) wheeze, adjusted 1.18 (0.93–1.51) asthma, adjusted	Outdoor levels at the home of subjects were estimated using a validated model. Reported associations refer to disease status at two years. Estimates of similar size obtained for highly correlated pollutants $PM_{2.5}$ and soot. Strongest association seen for ear, nose and throat infections and air pollutants.
8.5 μg/m^3 (range of annual averages 19–67 μg/m^3)	0.94 (0.79–1.12) wheeze, adjusted 1.24 (1.02–1.51) dry cough at night, adjusted	GIS-based modelling of exposure at the birth address. Comparable effect estimates obtained for $PM_{2.5}$ and soot. Stronger effect estimates obtained at age of 1 year (1.36 (1.07–1.74) dry cough at night, adjusted), especially in males.
10 μg/m^3 (range of 4-week measurements 6–46.7 μg/m^3)	1.20 (0.90–1.60), adjusted	Analyses used estimated winter-time averages outside the children's homes; range of these exposures not presented. Stronger effects for children who did not fulfil the criterion for recurrent wheeze until their second year of life. Interaction between nitrogen dioxide and exposure to environmental tobacco smoke.
1 ppb (range of 4-year average 4.2–8.0 ppb)	1.02 (1.00–1.03) between community, adjusted 1.07 (1.02–1.13) between community, adjusted	Associations of similar strength were seen for $PM_{2.5}$ and elemental carbon. The effect of nitrogen dioxide was independent of adjustments for PM_{10}, $PM_{10-2.5}$, acids and elemental carbon. Co-linearity of the effect was observed for ozone, $PM_{2.5}$ and elemental carbon
34.6 ppb (range of 8-year average 4–39 ppb)	–95 ml (–189 –1 ml) FVC, adjusted –101ml (–165–38 ml) FEV_1, adjusted –211 ml/s (–378–44 ml/s) MMEF, adjusted	Effects on FVC and FEV_1 were largest for acid vapours, which were highly correlated with nitrogen dioxide.

Outdoor population-based studies: long-term effects

Studies of long-term health effects have assessed the association between nitrogen dioxide and morbidity and mortality in children and adults. These studies have assessed the health effects associated with both between- and within-area variability of nitrogen dioxide. Misclassification of exposure is a major concern in

Table 4. Long-term effects of nitrogen dioxide: cancer risks in selected studies

Reference	Area, population, period	Outcome
Feychting, Svensson & Ahlbom *(184)*	142 patients with childhood cancer and 550 controls	Cancer (risk ratio)
Nyberg et al. *(185)*	1042 patients with lung cancer and 2364 controls aged 40–75 years, Stockholm County, Sweden, 1950–1990	Lung cancer (risk ratio)
Raashou-Nielsen et al. *(186)*	1989 children with leukaemia, tumour of the central nervous system or malignant lymphoma and 5506 control children, Denmark, 1968–1991	Leukaemia, tumour of the central nervous system or malignant lymphoma (risk ratio)
Filleul et al. *(187)*	14 284 adults recruited in 24 areas of 7 French cities (1974–1976), 25-year mortality follow-up based on death certificates	Lung cancer mortality (hazard ratio)
Hoek et al. *(188)*	5000 adults in the Netherlands aged 55–69 years, 8-year follow-up, 1986–1994	Lung cancer mortality (hazard ratio)
Pope et al. *(189)*	Approximately 409 000 to 493 000 adults in the United States from 78 metropolitan areas (nitrogen dioxide data as of 1980) or from 101 metropolitan areas (nitrogen dioxide data as of 1982–1998)	Lung cancer mortality (relative risk)

these studies, owing to the fact that (*a*) by design, area-specific estimates neglect the (often high) spatial variability of nitrogen dioxide within the area (city or residential area) and (*b*) these estimates only capture part of the individual exposure, disregarding contributions from transport, work/school, domestic appliances, hobbies, etc. In addition, studies of spatial variability are faced with the potential for uncontrolled confounding by other variables, which include risk factors of the considered diseases and in particular other traffic-related pollutants. Tables 3–5 list the results of selected studies on the long-term effects of nitrogen dioxide.

Nitrogen dioxide unit (mean)	Nitrogen dioxide effect estimate (95% CI)	Comments
Annual averages, categories of quartiles	No estimate for continuous exposure given	Range of nitrogen dioxide exposure is not reported. A relative risk estimate of 2.7 (95% CI 0.9–8.5) was found for total cancer at nitrogen dioxide concentrations of 50 μg/m^3 or higher compared to 39 μg/m^3 or lower. At 80 μg/m^3 the relative risk was 3.8 (95% CI 1.2–12.1).
10 μg/m^3 (modelled 10-year average)	1.10 (0.97–1.23) adjusted	Full range of exposure not reported. Results were robust against consideration of sulfur dioxide concentrations. There might be a suggestion of a threshold at around 30 μg/m^3 nitrogen dioxide.
Modelled (range 1.5–28 ppb)	No estimate for continuous exposure given	Nitrogen dioxide and benzene were modelled based on a validated model at residential address for pregnancy and childhood. Exposure is expressed per 1000 ppb-person-days. No overall increased risk observed, but malignant lymphomas were increased in association with exposure to nitrogen dioxide and benzene during pregnancy. Risk increases across quartiles and positive test for trend.
10 μg/m^3 (range 12–61 μg/m^3; after exclusion (18 areas) range 12–32 μg/m^3)	24 areas: 0.97 (0.85–1.10) 18 areas: 1.48 (1.05–2.06), both adjusted	No validation of cancer cases; no association with other correlated pollutants and lung cancer observed.
30 μg/m^3 (range of annual averages 14.7–67.2 μg/m^3)	1.25 (0.42–3.72) adjusted	Only 60 cases were identified; no validation of cancer cases. Estimates are for background and local concentrations combined.
Increment not given (mean (SD) 1980: 27.9 ppb (9.2 ppb))	Estimates only reported as figure	No association observed for nitrogen dioxide but observed for $PM_{2.5}$. Neither increments nor size of effects are reported.

Asthma, respiratory disorders and atopy

A large number of studies have assessed the association between respiratory morbidity in adults and children, assessing nitrogen dioxide concentrations on an area level, at the children's school or at home. Studies include measurements of nitrogen dioxide or modelled nitrogen dioxide concentrations. Both cross-sectional and cohort studies have been conducted. In the text below, special attention is paid to the cohort studies, as they could be regarded to be the most reliable basis for setting air quality guidelines.

Table 5. Long-term effects of nitrogen dioxide: fetal effects in selected studies

Reference	Area, population, period	Outcome
Liu et al. *(190)*	229 085 births in Vancouver, Canada, 1986–1998	Preterm birth, low-birth-weight birth, intrauterine growth retardation (odds ratio)
Wilhelm & Ritz *(191)*	13 464 pre-term births and 21 124 controls, 3771 term low-birth-weight births and 26 351 controls, Los Angeles, 1994–1996	Preterm birth or term low-birth-weight birth (odds ratio)
Dales et al. *(192)*	12 Canadian cities, daily number of sudden infant deaths (n = 1556), 1984–1999	Sudden infant death (relative risk)

In 1992, a Japanese cohort study assessed the impact of air pollution over a three-year period in 842 children age 10 years in 7 communities (*179*). Three-year average nitrogen dioxide concentrations ranged between 7 and 31 ppb. Incidence of asthma and wheeze were low in these communities, ranging between 0% and 7%. For wheeze incidence the odds ratio was 1.76 per 10-ppb increase in the three-year average at community level (95% CI 1.04–3.23), while for asthma incidence it was 2.10 (95% CI 1.10–4.75). These estimates were obtained while adjusting for sex, history of allergy, respiratory disease under two years of age, breastfeeding, parental history of allergy, indoor nitrogen dioxide concentrations, parental smoking, and use of a non-vented heater during the winter. Other air pollutants were not considered.

Cohort studies have been conducted in birth cohorts, assessing the incidence of asthma and respiratory symptoms at two years of age in the Netherlands *(180)* and Germany *(181)*. Also, a nested case–control study was conducted in Sweden *(182)*. A birth cohort study in rural and urban communities in the Netherlands was conducted that included 3745 children aged two years *(180)*. Nitrogen dioxide concentrations at the home address were modelled, based on a validated model, and ranged between 12 μg/m^3 and 58 μg/m^3 annual averages. Adjusted odds ratios for a 10-μg/m^3 increase in nitrogen dioxide were 1.13 for wheeze (95% CI 0.99–1.29) and 1.18 for asthma (95% CI 0.93–1.51). Nitrogen dioxide concentrations were highly correlated with estimated $PM_{2.5}$ and soot concentrations and the effects were not to be disentangled. A birth cohort study of 1757 children living in Munich, Germany, assessed the incidence of respiratory symptoms at two years of age *(181)*. Nitrogen dioxide concentrations at the home

Nitrogen dioxide unit (mean)	Nitrogen dioxide effect estimate (95% CI)	Comments
10 ppb	1.08 (0.99–1.17) preterm birth, adjusted, last month 1.05 (1.01–1.10) intrauterine growth retardation, adjusted, first month	Full range of exposure not reported. Similar results observed with other pollutants (sulfur dioxide and carbon monoxide). Pollutants were highly correlated.
1 pphm	1.05 (1.02–1.08) preterm birth, adjusted 1.06 (1.01–1.11) term low-birthweight birth, adjusted	Nitrogen dioxide concentrations were taken from the best station near to the home address. Estimates of nitrogen dioxide were reduced to null if traffic density was considered in the same model.
10.9 ppb (range of mean over study period 9.6–25.8 ppb)	1.15 (1.07–1.24), 3-day average, adjusted	Nitrogen dioxide concentrations were taken from the best station near to the home address. Estimates of nitrogen dioxide were reduced to null if traffic density was considered in the same model.

address were modelled, based on a validated model, and ranged between 19 and 67 μg/m^3 annual averages. Adjusted odds ratios for an 8.5-μg/m^3 increase in nitrogen dioxide were 0.94 for wheeze (95% CI 0.79–1.12) and 1.24 for dry cough at night (95% CI 1.02–1.51). Nitrogen dioxide concentrations were highly correlated with estimated $PM_{2.5}$ and soot concentrations and the effects were not to be disentangled. A nested case–control study in 540 two-year-old children (181 with recurring wheeze and 359 age-matched controls) were selected based on a birth cohort from Sweden (n = 4089) *(182)*. Four-week measurements outside the children's homes during October–March (winter) ranged between 6 μg/m^3 and 47 μg/m^3 nitrogen dioxide. The odds ratio of recurrent wheeze at two years of age was 1.20 for a 10-μg/m^3 increase in nitrogen dioxide (95% CI 0.90–1.60).

While the cohort studies suggest that there might be an association between annual average concentrations of nitrogen dioxide and wheeze or asthma, the results of earlier cross-sectional studies are mixed. For asthma diagnoses and symptoms, there are nine cross-sectional studies showing positive *(193–201)* and four showing negative associations *(202–205)*. Generally, the likelihood of detecting a positive association increased when studies considered within-area variability of nitrogen dioxide *(196–200)*.

Seven studies showed associations between nitrogen dioxide and bronchitis and cough *(195–205)*. The cohort study within the Southern California Children's Study assessed the impact of air pollution on the incidence of bronchitic symptoms, using an annual questionnaire from 1996 to 1999 in 475 children with asthma aged 9–13 years living in 12 Southern California communities *(127)*. The four-year average concentrations of nitrogen dioxide ranged between 4 ppb and

38 ppb. Bronchitic symptoms were frequent in the asthmatic children, being 37% in girls and 40% in boys. The odds ratio for bronchitic symptoms was 1.02 per 1-ppb increase in nitrogen dioxide in the four-year average on the community level (95% CI 1.00–1.03). For variation of nitrogen dioxide within a community over time, a larger effect estimate was obtained (odds ratio 1.07 per 1 ppb nitrogen dioxide yearly average; 95% CI 1.02–1.13). All results were adjusted for age, sex, race, mothers' and children's smoking history, and community or within-community nitrogen dioxide concentration. This indicates that the sum of nitrogen dioxide exposure, both at the community level and between different locations in the community, would more adequately describe the association. Between communities there was a high correlation of nitrogen dioxide with $PM_{10,}$ $PM_{2.5}$ and organic and elemental carbon, but on the within-community level the correlations were weaker. Adjusting for other particulate pollutants, both on the between- as well as on the within-community levels, substantially reduced the association of nitrogen dioxide.

To summarize, the cohort studies seem to suggest that there is an association between concentrations of nitrogen dioxide at the home address and the incidence of asthma in children. The limitation is that the available data from cohort studies mostly assesses children at two years of age. While the studies consider important individual risk factors, none is able to attribute the effects to nitrogen dioxide concentrations per se. They can be regarded as substantial evidence for a long-term impact of traffic-related pollution on the development of asthma, while being unable to identify responsible air pollutant components. In addition, evidence was found that not only asthma but also cough and bronchitis symptoms may be augmented. Again, however, these effects cannot with sufficient certainty be attributed to nitrogen dioxide alone.

Lung function

Cohort studies from California indicate an association between nitrogen dioxide and reduced lung function in children *(125,126,183)*. These studies are well-designed, have a long follow-up, consider a rather broad range of exposures, and provide the best evidence available to date. Children in Southern California were studied to assess chronic respiratory effects due to long-term exposure to four pollutants (ozone, PM, acids and nitrogen dioxide) in 12 communities. Follow-up of the children after four years showed significant deficits in growth of lung function associated with exposure to PM_{10}, $PM_{2.5}$, nitrogen dioxide and inorganic acid vapour *(125)*. The Californian group also studied changes in lung function of participants (n = 110) who had moved to other communities *(206)*. They found reductions in annual lung function growth rates (FEV_1, maximum mid-expiratory flow (MMEF) and PEF) among children in areas with more pollution, and improvements among children who had moved to less polluted areas. There was no evidence of systematic differences between children who

stayed or moved out of their communities. These results were confirmed in a recent publication *(183)* in 1759 fourth-graders enrolled in 1993 and followed for eight years until 2001. Four-year averages ranged from 4 ppb to 39 ppb nitrogen dioxide across the communities. Across the range of 35 ppb, FVC decreased –95 ml (95% CI –189 to –1 ml), FEV_1 decreased –101 ml (95% CI –165 to –38 ml) and MMEF decreased –211 ml/s (95% CI –378 to –44 ml/s) after adjustment for known risk factors, including log-transformed height, quadratic function of body mass index, sex, race, and interactions between sex and log-transformed height, sex and asthma, and sex and race. The associations were observed down to 20 $\mu g/m^3$ nitrogen dioxide. This study found strong evidence that lung function growth was slower in communities with high levels of nitrogen dioxide, acid vapour, $PM_{2.5}$ and elemental carbon. Nitrogen dioxide was highly correlated with other pollutants, particularly with elemental carbon ($r = 0.94$) and acid vapour ($r = 0.87$). This again points to the contribution of traffic as a major source of pollution in Southern California. Although only 747 of the 1759 children were followed over eight years, the dropout was not related to lung function measurements at the start of the study and therefore it is unlikely that a bias might have occurred.

For adults, the Swiss SAPALDIA cross-sectional study (Study on Air Pollution and Lung Diseases in Adults) assessed average levels of nitrogen dioxide exposure in eight study communities and its association with lung function (FVC and FEV_1) *(207)*. Regional averages of passive sampler measurements were computed, based on a random sub-sample of SAPALDIA participants in 1993. This analysis showed that an increase in average nitrogen dioxide between different residential zones in the same community was associated with a change in average FVC. Estimates were even larger where personal exposure estimates were concerned.

In summary, the Southern California Children's Health Study provides evidence of the effect of nitrogen dioxide on lung function growth, and suggests that lung function values below the 80% predicted might be as much as five times more likely in polluted communities than in communities with low pollution. Given the fact that lung function values persist throughout life, these decrements will have a lifelong impact on the health of those affected. Evidence from Europe supports an association between nitrogen dioxide and lung function in adults. However, doubt remains as to whether those effects are attributable to nitrogen dioxide per se, as other highly correlated measures of traffic-related PM showed associations of similar strength.

Cancer

Studies have assessed the association between exposure to nitrogen dioxide or nitrogen oxides and cancer in Europe. These exposures were often dominated by traffic-related pollution and therefore the carcinogenic components might include diesel particles, benzene or polycyclic aromatic hydrocarbons.

A population-based case–control study with 1042 lung cancer patients and 2364 controls was conducted among 40–75-year-old male residents of Stockholm County from 1950 to 1990 *(185)*. Local annual source-specific air pollution levels for nitrogen oxides/nitrogen dioxide and sulfur dioxide were estimated using validated dispersion models and linked to residential addresses. An increase of 10 μg/m^3 average traffic-related nitrogen dioxide exposure over 10 years was associated with lung cancer (odds ratio 1.10 (95% CI 0.97–1.23)) after adjusting for tobacco smoking, socioeconomic status, residential radon and occupational exposures. There could be evidence for suggesting a threshold of around 30 μg/m^3 nitrogen dioxide.

From a population of 127 000 children living within 300 m of power transmission lines in Sweden, 142 cases of childhood cancer were identified, including 39 cases of leukaemia and 33 cases of central nervous system tumours *(184)*. Approximately four referents per case were selected at random from the study base. Exposure was estimated and defined by the 99th percentile of the nitrogen dioxide content of the outdoor air for one-hour averages over one year; the range of nitrogen dioxide concentrations was not reported. The study observed an increased risk of childhood cancer at high nitrogen dioxide concentrations. A relative risk estimate of 2.7 (95% CI 0.9–8.5) was found for total cancer at nitrogen dioxide concentrations of 50 μg/m^3 or higher compared to 39 μg/m^3 or lower. The number of cases was relatively small owing to the rareness of the diseases.

A registry-based case–control study in Denmark, involving 1989 children with cancer and 5506 controls, calculated the mean benzene and nitrogen dioxide concentrations at the front door of every address of the mother during the pregnancy and the address of the child for the time between birth and the diagnosis of cancer *(186)*. Leukaemia and tumours of the central nervous system were not associated with any exposure indicator. A higher risk of lymphoma in the children was reported for high nitrogen dioxide concentrations during pregnancy. Although there was a significant trend across categories, the data are not presented in a way conducive to abstracting an exposure–response estimate per unit increase in nitrogen dioxide.

Filleul et al. found a positive association between nitrogen dioxide concentrations and cancer mortality in a 25-year follow up of 14 284 adults in seven French cities. This association was observed after excluding areas with a high potential for misclassifying exposures of individuals resident in these areas by unrealistically high nitrogen dioxide measurements at traffic sites *(187)*.

Since nitrogen dioxide per se is considered here, the studies by Nafstad and colleagues (showing associations with lung cancer and lung cancer mortality for modelled nitrogen oxides exposure at the home address) are not covered here *(208,209)*. This is a debatable decision, however, since if there is indeed a causal association between nitrogen dioxide and cancer then of course studies assessing nitrogen oxides would also be able to demonstrate this effect. The suspicion that

other PM-associated pollutants are more likely to be responsible agents is also supported by the null finding of the American Cancer Society Study for nitrogen dioxide in the presence of a positive association between $PM_{2.5}$ and lung cancer mortality *(189)*.

The evidence presented in this section suggests that traffic-related pollution may be associated with childhood cancer and lung cancer in adults, but no compelling evidence is available to date to attribute these associations to nitrogen dioxide per se. In addition, the studies from Europe may demonstrate that the association between traffic-related pollution and cancer is better depicted by using within- rather than between-area variation in nitrogen dioxide.

Fetal and reproductive effects

In California, 3771 cases of low birth weight at term, 3509 cases of preterm low birth weight, 13 464 cases of preterm birth and 26 351 control births were evaluated *(191)*. In addition to ambient air pollution concentrations, this recent study also included a distance-weighted traffic density measure of exposure. Nitrogen dioxide concentrations were associated with low birth weight at term and preterm births. However, the results for nitrogen dioxide were no longer statistically significant in multivariate models including nitrogen dioxide and quintiles of the distance-weighted traffic density. Associations between air pollution and birth defects were also reported for 4570 cases and 3667 controls, but no clear role of nitrogen dioxide was identified *(210)*.

A recent Canadian study examined the association between preterm birth, low birth weight and intrauterine growth retardation among singleton live births and ambient concentrations of sulfur dioxide, nitrogen dioxide, carbon monoxide and ozone in Vancouver, Canada, between 1985 and 1998 *(190)*. Multiple logistic regression models were used to estimate odds ratios and 95% confidence intervals for these effects. Low birth weight was not associated with nitrogen dioxide exposure. Preterm birth was associated with exposure to nitrogen dioxide during the last month of pregnancy, while intrauterine growth retardation was associated with exposure to nitrogen dioxide during the first month of pregnancy. Another study reported an association between nitrogen dioxide concentrations and sudden infant death syndrome, based on data from 12 Canadian cities *(192)*. A case–control study of 169 cases of sudden infant death syndrome and 169 matched controls suggested no effect of nitrogen dioxide during pregnancy, except on the day before the onset of the syndrome, suggesting a short-term effect *(211)*. A recent study from China (Province of Taiwan) reported an association between low birth weight and nitrogen dioxide concentrations, based on data from 92 288 full-term live births between 1995 and 1997 *(212)*. No continuous estimates of the nitrogen dioxide effects were provided, and nitrogen dioxide effects were smaller than those observed for sulfur dioxide.

In summary, air pollution exposure during pregnancy may be related to low birth weight at term, intrauterine growth retardation, preterm birth and perinatal mortality. There seems to be some evidence for an association between traffic-related air pollution and fetal effects. However, it is unclear whether there is an independent effect of nitrogen dioxide per se on reproductive and birth effects.

(Long-term) mortality

Recent data from Europe suggested that long-term concentrations of nitrogen dioxide or nitrogen oxides were associated with an increased risk of all-cause mortality *(187,188,209)*. However, none of the studies found evidence that nitrogen dioxide per se, but rather particulate pollution especially from traffic sources, seemed to be responsible for the observed associations. A study on selected United States retirees with a diagnosis of hypertension did suggest an effect of nitrogen dioxide on overall mortality *(213)*, but in the most recent follow-up of the American Cancer Society cohort no association between urban background concentrations of nitrogen dioxide and all-cause mortality was observed *(189)*. The association between PM and long-term mortality is reviewed in detail in Chapter 10. As reasoned before, the studies from Europe may demonstrate that the association between traffic-related pollution and mortality is better depicted by using within- rather than between-area variation in nitrogen dioxide.

Indoor studies

Several epidemiological investigations have been conducted in indoor settings, and the results are controversial. An increased incidence of lower respiratory symptoms among children in relation to indoor nitrogen dioxide has been suggested from a meta-analysis of indoor studies conducted in 1992 *(214)*. It concluded that long-term exposure to nitrogen dioxide is associated with a higher prevalence of respiratory symptoms in children under 12 years of age (odds ratio 1.2, 95% CI 1.1–1.3 for an increase in nitrogen dioxide exposure of 30 $\mu g/m^3$). This meta-analysis, however, relied on a limited number of rather heterogeneous studies.

In a follow-up study of a birth cohort in Albuquerque, New Mexico, with a very comprehensive surveillance method to detect respiratory illness during the first year of life, indoor nitrogen dioxide measurements were not associated with incidence of illness *(215)*. However, levels of nitrogen dioxide were very low (median around 10 ppb) in this study, consistent with the low frequency of use of gas stoves in that community. A multicentre cohort study of 1611 newborn babies was conducted in Europe *(216)* to assess the association between indoor nitrogen dioxide and lower respiratory tract infections during the first year of life, involving a broad range of indoor nitrogen dioxide exposures. Nitrogen dioxide was measured with passive diffusion tubes placed in the living room for two weeks when infants were approximately three months old. The outcomes were validated

using clinical records or nasopharyngeal lavage and culture. The cumulative rates of infection were unrelated to nitrogen dioxide levels (corresponding medians in the three centres being 6, 46 and 12 ppb, respectively) in all three centres (all odds ratios being around 1).

By contrast, some recent investigations have suggested specific effects of nitrogen dioxide among children with asthma or at risk of asthma because of family history. Chauhan et al. *(217)* followed a cohort of asthmatic children in Great Britain, measuring personal nitrogen dioxide exposures weekly for up to 13 months, obtaining viral cultures for each illness episode and assessing the severity of the illness. Personal exposure to nitrogen dioxide was associated with more severe illness and an increased risk of virus-related asthma morbidity in this study. In a cohort of newborns with an asthmatic sibling, measured indoor nitrogen dioxide levels (mainly from gas stoves) were associated with increased risk of wheeze and cough in the first year of life *(218)*. A strong association between indoor nitrogen dioxide and respiratory symptoms among infants has recently been reported from the United States (New England) *(219)*. The investigators addressed an important issue, namely exposure to nitrous acid, which is a primary product of combustion and is also formed when nitrogen dioxide reacts with water; it may thus play an important confounding role *(220)*. The study was based on 768 infants at risk of developing asthma because of an older asthmatic sibling, and estimated the independent effects of exposure to nitrogen dioxide and nitrous acid on respiratory symptoms during the first year of life. Nitrogen dioxide and nitrous acid concentrations were measured once using passive samplers. Infants living in homes with a nitrogen dioxide concentration exceeding 17.4 ppb (highest quartile) had more days with wheeze (rate ratio 2.2; 95% CI 1.4–3.4), persistent cough (1.8; 1.2–2.7), and shortness of breath (3.1; 1.8–5.6) than infants in homes with nitrogen dioxide concentrations lower than 5.1 ppb (lowest quartile), controlling for nitrous acid concentration. Nitrous acid exposure was not independently associated with respiratory symptoms in this study. Finally, in a recent study, the association of indoor nitrogen dioxide exposure with respiratory symptoms among 728 asthmatic children (under 12 years of age) was studied using Palmes tubes. Mean nitrogen dioxide was 25.9 (SD18.1) in houses with gas stoves. Each 20-ppb increase in nitrogen dioxide increased the frequency of wheeze (odds ratio 1.52 (1.04–2.21)) or chest tightness (odds ratio 1.61(1.04–2.49)) *(221)*.

With regard to the effects of indoor nitrogen dioxide among adults, a study in the United Kingdom found that women, and particularly atopic women, were at an increased risk of symptoms on exposure to gas cooking appliances *(222)*. In a subsequent study *(223)*, 276 adults provided information on respiratory symptoms and lung function, and home levels of nitrogen dioxide and nitrous acid and outdoor levels of nitrogen dioxide were measured. An increase in indoor nitrous acid was associated with a decrease in FEV_1 and FEV_1/FVC. Measures of indoor

nitrogen dioxide were correlated with nitrous acid (r = 0.77) but no significant association of indoor nitrogen dioxide with symptoms or lung function was observed. The authors concluded that inconsistencies between studies examining health effects of nitrogen dioxide and the use of gas appliances may be related to a failure to account for the association with nitrous acid.

In summary, even studies conducted indoors are not free of the potential confounding effect of particulate air pollution since, in addition to nitrogen dioxide, burning natural gas in stoves or cooking produces fine and ultrafine particles. Nitrous acid, humidity or moulds may also play a confounding role. In addition, measurements of nitrogen dioxide exposure indoors mainly rely on passive sampling devices installed over some weeks and, considering the large variability in individual use of indoor nitrogen dioxide sources and in ventilation over the year, it is difficult to estimate long-term exposure. Given the above caveats, however, among infants and children with asthma or at risk of developing asthma, the frequency of respiratory symptoms is associated with increased nitrogen dioxide concentrations.

Evaluation of human health risks

Exposure

There is considerable temporal as well as spatial variability in nitrogen dioxide levels in the outdoor environment. Natural background annual mean concentrations range from 0.4 to 9.4 μg/m^3. Outdoor urban levels have an annual mean ranging from 20 to 90 μg/m^3 and an hourly maximum ranging from 75 to 1015 μg/m^3. Levels indoors where there are unvented gas combustion appliances may average more than 200 μg/m^3 over a period of several days. A maximum 1-hour peak may reach 2000 μg/m^3. For briefer periods, even higher concentrations have been measured.

Health risk evaluation

Toxicological data support the notion that nitrogen dioxide can induce toxic airway effects, including reduced host defence against microbiological agents and enhanced bronchial hyperresponsiveness in asthmatics to allergen and irritant stimuli. However, without exception, these effects have been described in experimental studies following exposure to nitrogen dioxide concentrations far beyond levels cited in current guidelines. There are no new studies that address these issues at concentrations that are considered to be environmentally relevant and that separate the effects of nitrogen dioxide from those of other pollutants.

Epidemiological studies of nitrogen dioxide exposures from indoor and outdoor air are limited by being unable to separate the effects of nitrogen dioxide from those of other pollutants, especially fine particles. The risk estimates in many studies were greatly reduced and often became non-significant after adjusting for

particles. In some studies, however, the strongest effect was found for nitrogen dioxide itself, while PM had a weaker or no effect. In particular, stronger indications of an independent effect of nitrogen dioxide come from studies on hospital admissions or emergency department visits for respiratory and cardiovascular diseases, studies on asthma aggravation, and from evaluating indoor effects, especially among asthmatics and infants at risk of asthma.

Nitrogen dioxide concentrations closely follow vehicle emissions in many situations, so nitrogen dioxide levels are generally a reasonable marker of exposure to traffic-related emissions. Health risks from nitrogen oxides may potentially result from nitrogen dioxide itself, correlated exhaust components such as ultrafine particles and hydrocarbons, or nitrogen dioxide chemistry products, including ozone and secondary particles. The issue is complicated by the fact that PM_{10} or $PM_{2.5}$ might be indicators for regionally transported, rather homogeneously distributed particles as well as locally produced, rather non-homogeneously distributed combustion particles. Nitrogen dioxide is often recognized as an indicator of locally produced particles, mainly from mobile sources. This also seems to be the case in the Southern California Children's Air Pollution Study, which on the one hand provides evidence for a strong nitrogen dioxide health effect, but on the other reports the impossibility of disentangling the effects of nitrogen dioxide from the effects of elemental carbon. The same issue applies to assessing the role of nitrogen dioxide in inducing respiratory disease in children.

In conclusion, nitrogen dioxide concentrations are often used to establish spatial variability in air pollution concentrations from mobile sources and remain inseparable from the often unmeasured particle emissions from combustion sources, and in particular from mobile sources. Therefore, it is difficult to determine whether the effects observed for nitrogen dioxide and PM are the independent effects of the gaseous pollutant nitrogen dioxide and of PM, or are independent effects of locally produced fine and ultrafine carbonaceous particles and of regionally transported accumulation-mode particles.

Guidelines

Evidence from animal toxicological studies indicates that long-term exposure to nitrogen dioxide at concentrations above current ambient concentrations has adverse effects. In population studies, nitrogen dioxide has been associated with adverse health effects even when the annual average nitrogen dioxide concentration complied with the WHO annual guideline value of 40 $\mu g/m^3$ *(121)*. Also, some indoor studies suggest effects on respiratory symptoms among infants at concentrations below 40 $\mu g/m^3$. Together, these results support a lowering of the annual nitrogen dioxide guideline value. However, since nitrogen dioxide is an important constituent of combustion-generated air pollution and is highly correlated with other primary and secondary combustion products, it is unclear to what extent the health effects observed in epidemiological studies are attributable

to nitrogen dioxide itself or to other correlated pollutants. The current scientific literature, therefore, has not accumulated sufficient evidence to change WHO's 2000 guideline value of 40 μg/m^3 for annual nitrogen dioxide concentration *(121)*.

Many short-term experimental human toxicology studies show acute health effects at levels higher than 500 μg/m^3, and one meta-analysis has indicated effects at levels exceeding 200 μg/m^3. The current scientific literature has not accumulated evidence to change from the WHO guideline value of 200 μg/m^3 for 1-hour nitrogen dioxide concentration *(121)*.

Commentary

As an air pollutant, nitrogen dioxide has various roles that are often difficult or sometimes impossible to separate from each other.

- Animal and human experimental toxicology indicates that nitrogen dioxide is itself – in short-term concentrations exceeding 200 μg/m^3 – a toxic gas with significant health effects.
- Numerous epidemiological studies have used nitrogen dioxide as a marker for the air pollution mixture of combustion-related pollutants, in particular traffic exhaust or indoor combustion sources. In these studies, the observed health effects might also have been associated with other combustion products, such as ultrafine particles, nitric oxide, PM or benzene. Other studies – both outdoors and indoors – have attempted to focus on the health risks of nitrogen dioxide, yet the contributing effects of other, highly correlated co-pollutants were often difficult to rule out.
- Most atmospheric nitrogen dioxide is emitted as nitric oxide, which is rapidly oxidized by ozone to nitrogen dioxide. Nitrogen dioxide, in the presence of hydrocarbons and ultraviolet light, is the main source of tropospheric ozone and of nitrate, which forms an important fraction of the ambient air $PM_{2.5}$ mass.

The present guideline was set to protect the public from effects on health of nitrogen dioxide gas itself. The rationale for this is that, because most abatement methods are specific to nitrogen oxides, they are not designed to control other co-pollutants and may even increase their emissions. If, instead, nitrogen dioxide is monitored as a marker for the concentrations and risks of the complex combustion-generated pollution mixtures, an annual guideline value lower than 40 μg/m^3 should be used instead.

There is still no robust basis for setting an annual average guideline value for nitrogen dioxide through any direct toxic effect. Epidemiological evidence has emerged, however, that increases the concern over health effects associated with outdoor air pollution mixtures that include nitrogen dioxide. These studies have shown, for example, that bronchitic symptoms of asthmatic children increase in

association with annual nitrogen dioxide concentrations, and that reduced lung function growth in children is linked with increased nitrogen dioxide concentrations within communities already at current North American and European urban ambient air levels. Recently published studies document that nitrogen dioxide, as a marker of complex mixtures of traffic-related combustion pollution, can have higher spatial variation than particle mass. In addition, these studies reported adverse effects on the health of children living in the areas characterized by higher levels of nitrogen dioxide, even when the overall level was low. Furthermore, recent studies on indoor nitrogen dioxide concentrations have added evidence on adverse effects of nitrogen dioxide on respiratory symptoms in children. WHO's annual average nitrogen dioxide guideline value of 40 μg/m^3 *(121)* is within the exposure ranges reported in these investigations. They also show that these associations cannot be completely explained by co-exposure to PM, but that other components in the mixture (such as organic carbon and nitrous acid vapour) might explain part of the association. Since such components are not routinely measured, and nitrogen dioxide concentrations in ambient air are readily available, it seems reasonable to retain a prudent annual average limit value for nitrogen dioxide. Such a limit takes into account that there may be direct toxic effects of chronic nitrogen dioxide exposure at low levels. In addition, the annual guideline value may help to control complex mixtures of combustion-related pollution (mainly from road traffic).

In experimental studies, the lowest level of nitrogen dioxide exposure reported in more than one laboratory shows a direct effect on pulmonary function in asthmatics at 560 μg/m^3. Studies of bronchial responsiveness among asthmatics indicate an increase in responsiveness at levels upwards from 200 μg/m^3. The WHO short-term nitrogen dioxide guideline of 200 μg/m^3 *(121)* is not challenged by more recent studies, and should therefore remain.

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13. Sulfur dioxide

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General description

Historically, sulfur dioxide and PM derived from the combustion of fossil fuels have been the main components of air pollution in many parts of the world. The most serious problems have been experienced in large urban areas where coal has been used for domestic heating or for poorly controlled combustion in industrial installations. In such situations, the complex of pollutants has generally been considered collectively, drawing on findings from epidemiological studies carried out decades ago in areas formerly heavily polluted. Guidelines developed in this way had been related to averaging times of 24 hours in respect of acute effects and one year in respect of chronic effects.

Separate attention has been paid to sulfur dioxide alone, based largely on findings from controlled human exposure studies. These allow guidelines to be developed in terms of shorter averaging periods of the order of one hour. These are relevant to exposures to peak concentrations that may arise from sources burning coal or heavy oil, whether or not accompanied by substantial concentrations of PM. Epidemiological studies published in the last decade provide suggestive evidence on the health effects of sulfur dioxide. Thus, a section has been introduced in this revision focusing on epidemiological results in locations where the sources of sulfur dioxide are mainly motor vehicles and various industries.

Sulfur dioxide is derived from the combustion of sulfur-containing fossil fuels and is a major air pollutant in many parts of the world. Oxidation of sulfur dioxide, especially at the surface of particles in the presence of metallic catalysts, leads to the formation of sulfurous and sulfuric acids. Neutralization, by ammonia, leads to the production of bisulfates and sulfates.

Sulfur dioxide is a colourless gas that is readily soluble in water. Sulfuric acid is a strong acid formed from the reaction of sulfur trioxide (SO_3) with water. Sulfuric acid is strongly hygroscopic. As a pure material it is a colourless liquid with a boiling point of 330 °C. Ammonium bisulfate (NH_4HSO_4), which is also a strong acid but is less acidic than sulfuric acid as a pure material, is a crystalline solid with a melting point of 147 °C. The formation of very small droplets of sulfuric acid occurs by nucleation. Many vapours are able to condense on the surface of existing very fine nuclei and lead to the growth of composite particles. Sulfuric acid vapour, unlike many other vapours, exhibits the property of being able to condense and produce nuclei de novo.

Sources

Natural sources, such as volcanoes, contribute to environmental levels of sulfur dioxide. In most urban areas, man-made contributions are of the greatest concern. These include the use of sulfur-containing fossil fuels for domestic heating, stationary power generation and motor vehicles. In recent years the use of high-sulfur coal for domestic heating has declined in many European countries, and power generation and motor vehicles are now the predominant sources. This has led to a continued reduction in levels of sulfur dioxide in cities such as London, which were once heavily polluted. The use of tall chimneys at power stations has led to wider dispersion and dilution of sulfur dioxide. These changes in pattern of usage have led to urban and rural concentrations becoming more similar in the economically developed countries; indeed, in some areas, rural concentrations now exceed those in urban areas. In many developing countries, however, the use of high-sulfur coal is increasing for power production, as well as for domestic heating and cooking, and ground-level sulfur dioxide concentrations remain at very high levels.

Occurrence in air

As a result of changes in sources, annual mean levels of sulfur dioxide in the major cities of Europe have fallen since the second edition of *Air quality guidelines for Europe (1)* was published in 2000 and are now largely below 50 μg/m^3. Daily mean concentrations have also fallen and are now generally below 100 μg/m^3. Peak concentrations over shorter averaging periods may still be high, both in cities with a high use of coal for domestic heating and when plumes of effluent from power station chimneys fall to the ground (fumigation episodes). Transient peak concentrations of several thousand μg/m^3 may occur. Indoor concentrations of sulfur dioxide are generally lower than outdoor concentrations, since absorption occurs on walls, furniture and clothing and in ventilation systems. An exception is occupational exposure, where concentrations of several thousand μg/m^3 may occur.

Data on European concentrations of sulfur dioxide and deposition of other sulfur compounds are based either on national monitoring networks, which are largely concentrated in urban areas, or on cooperative programmes for the study of long-range transport of pollutants. Natural background concentrations of sulfur dioxide in rural areas of Europe are generally below 5 μg/m^3. The use of tall chimneys, which disperse emissions over wide areas, has led to this increasing to above 25 μg/m^3 in many areas.

Concentrations of sulfur dioxide in recent years in Asia vary from about 200 μg/m^3 in some Chinese cities to less than 20 μg/m^3 in others, such as Taipei and Hong Kong.

Conversion factors

1 ppm (20 °C, 1013 hPa) = 2660 μg/m^3
1 mg/m^3 = 0.3759 ppm

Routes of exposure

Inhalation is the only route of exposure to sulfur dioxide that is of interest with regard to its effects on health.

Toxicokinetics

Absorption of sulfur dioxide in the mucous membranes of the nose and upper respiratory tract occurs as a result of its solubility in aqueous media: 1 volume of water dissolves 45 volumes of sulfur dioxide at 15 °C. Absorption is concentration-dependent, with 85% absorption in the nose at 4–6 μg/m^3 and about 99% at 46 μg/m^3. Amdur *(2)* pointed out that at common ambient concentrations of sulfur dioxide, absorption in the upper airways may be inefficient.

Increased flow rates reduce the percentage of inspired sulfur dioxide absorbed in the nose and upper airways, and thus exercise promotes delivery to the smaller airways. Ammonia is found in the mouth (a product of bacterial metabolism) and may play a role in neutralizing acid aerosols. Sulfite and bisulfite are thought to be the major ions formed on absorption of sulfur dioxide. The key reactions are:

$$SO_2 + H_2O \rightarrow H_2SO_3 \quad (1)$$

$$H_2SO_3 + H_2O \rightarrow HSO_3 + H_3O \quad (2)$$

$$HSO_3 + H_2O \rightarrow SO_3 + H_3O \quad (3)$$

The pKa values of reactions 2 and 3 are 1.86 and 7.2, respectively. The pH of the surface fluid in the respiratory tract is 6.5–7.5, and thus appreciable amounts of both the bisulfite and the sulfite will be present. Absorbed bisulfite is converted to sulfate by molybdenum-dependent sulfite oxidase. The highest concentrations of this enzyme occur in the liver and kidney, while lower levels are found in the lung. The importance of sulfite oxidase in removing absorbed sulfur dioxide from the respiratory tract in humans requires further study, although rats deficient in sulfite oxidase are reported to be more sensitive than control animals to inhaled sulfur dioxide.

The sulfite ion is a reducing agent and reacts with oxidized glutathione in the surface fluid of the airways. Studies of the metabolism of sulfur dioxide have shown that sulfate is also produced from sulfite. The toxicological significance of this process is not yet known.

Health effects

Effects on experimental animals

The acute effects of sulfur dioxide at ambient concentrations may be conveniently studied by short-term exposure of human volunteers. The effects of long-term exposure to sulfur dioxide can, however, be studied only in experimental animals. At concentrations in excess of 28.6 mg/m^3 (10 ppm), prolonged exposure has been shown to produce damage to the epithelium of the airways. This may be followed by epithelial hyperplasia, a dose-related increase in goblet cells and hypertrophy of the submucosal glands. These changes are similar to those seen in chronic bronchitis in humans; prolonged exposure of rats and dogs to sulfur dioxide has been used to produce models of this disease.

In addition to the morphological changes mentioned above, slowing of ciliary transport of mucus has also been demonstrated, although only on exposure to high (858 mg/m^3 or 300 ppm) concentrations of sulfur dioxide. Effects were seen on exposure to much lower concentrations of sulfuric acid. Disruption of ciliary function has recently been shown on exposure of explanted human bronchial tissue to a combination of 572 μg/m^3 (200 ppb) sulfur dioxide and 752 μg/m^3 (400 ppb) nitrogen dioxide.

Studies in a range of species have shown that exposure to sulfur dioxide produces bronchoconstriction. Studies in guinea-pigs show responses in the same concentration range as has been shown to affect asthmatic volunteers (about 715 μg/m^3 or 0.25 ppm).

Studies by Amdur *(2)* have demonstrated that the effects of sulfur dioxide may be enhanced by simultaneous exposure to ultrafine particles. In particular, zinc oxide (2.5–5 mg/m^3) and sulfur dioxide (2860 μg/m^3 or 1 ppm) led to decreased lung volumes and carbon monoxide diffusing capacity in guinea-pigs. These changes were correlated with oedema and damage to epithelial and endothelial cells. Responses increased as the concentration of zinc oxide was raised. The formation of sulfuric acid on the surface of the ultrafine particles and the particles' delivery to the distal lung have been put forward as explanations of these effects. Re-analysis of air pollution data collected in London in the 1960s has shown a stronger relationship between concentrations of sulfuric acid aerosol and effects on health than with concentrations of black smoke or sulfur dioxide. These findings, and the association between high concentrations of sulfur dioxide, particles and water vapour during the London smogs prior to the 1970s, suggest that the health effects may have been caused by sulfuric acid delivered on the surface of fine and ultrafine particles.

Effects on humans

Controlled chamber experiments

A useful guide to the immediate effects of short-term exposures on pulmonary function has been provided from the results of controlled chamber experiments with volunteers. These have the advantage of accurate assessment of exposure, freedom from other pollutants and the availability of sensitive laboratory instruments for the measurement of effects, mainly in terms of lung function. Nevertheless, their limitations should also be recognized. Disadvantages include the small numbers of subjects who can be accommodated in any one study, uncertainties as to whether particularly sensitive people have been included, ethical limitations on the use of children, and restrictions placed on physical activity within the confines of the chamber and on duration of exposure *(3)*.

The general features that emerged from the many studies are the following.

- There appears to be a continuous spectrum of sensitivity to sulfur dioxide, some people being completely unaffected by concentrations that lead to severe bronchoconstriction in others. Asthmatics as a group are particularly sensitive, but otherwise the degree of sensitivity of normal subjects is not obviously related to other characteristics *(3–6)*.
- Being highly soluble, sulfur dioxide is readily absorbed in the upper respiratory tract and effects are enhanced if penetration to lower regions is increased (through mouth rather than nose breathing and through exercise that raises the amount and depth of inhalation). In chamber studies, exercise is introduced with bicycle ergonometers or treadmills *(3,7)*.
- Response to inhaled sulfur dioxide is rapid, the maximum effect usually being reached within a few minutes *(8)*. Continued exposure does not in general increase the response, and there is a tendency for it to decline gradually *(4)*. Chamber exposures have varied in duration, extending up to six hours in some cases *(9)* but more commonly being 10–15 minutes.
- Effects are generally short-lived. Lung function returns to normal after some minutes to hours, varying with the individual and the severity of the response.
- Chamber experiments are usually conducted at room temperature but some increase in response has been noted, at least among asthmatics, when sulfur dioxide is administered in cold dry air *(10)*.

In view of all these variable features it is difficult to draw a consistent picture of exposure–response relationships for pulmonary function, but the findings among normal subjects can be summarized as follows. Reductions in mean lung function values among groups of normal subjects at rest have been seen in 10-minute exposures at 4000 ppb (11 440 $\mu g/m^3$) *(11)* and at 5000 ppb (14 300 $\mu g/m^3$) *(4)*. No significant changes in group mean lung function have been seen below 1000 ppb (2860 $\mu g/m^3$) even with exercise, although there are examples

of airway resistance increasing in individuals at that value, with deep breathing *(4)*.

Findings among asthmatics can also be summarized. Such people appear to respond in a similar way to normal subjects, with development of bronchoconstriction, but at lower concentrations. Similarly, there are large variations in sensitivity, and while patients with severe asthma might not necessarily display the greatest sensitivity they would normally be excluded from experimental exposures.

Several studies have shown fairly large changes in mean values of lung function indices with 600 ppb (1716 μg/m^3) and heavy exercise *(11,12)* and with 500 ppb (1430 μg/m^3) and moderate or severe but not light exercise *(7)*. There are not necessarily clear thresholds, and for the purposes of guideline development interest focuses on the lower ranges of concentration, i.e. within those liable to occur in the ambient air. Several forms of exposure–response relationship have emerged from the literature *(3)*, each showing decreases in forced expiratory volume (FEV) or increases in airway resistance on a group mean basis when plotted against log sulfur dioxide concentration. One relatively straightforward example is given in the study by Linn et al. *(13)* examining the dose–response relationship of change in mean FEV_1 with increasing concentrations of sulfur dioxide with exercise (after subtracting the effect of exercise alone) in patients with moderate or severe asthma. Overall, the mean response at 400 ppb (1144 μg/m^3) has been definite though small, at around a 300-ml fall, whereas at 200 ppb (572 μg/ m^3) any change has been minimal and similar in magnitude to effects of exercise alone in clean air.

From the information published to date, the overall conclusion is that the minimum concentration evoking changes in lung function in exercising asthmatics is of the order of 400 ppb (1144 μg/m^3), although there is the one example of small changes in airway resistance in two sensitive subjects at 100 ppb (286 μg/ m^3). In evaluating this further, judgements are required regarding the clinical significance of such effects, the extent to which particularly sensitive subjects have been represented in the studies, the practical relevance of the enforced exercise required to enhance the effects, and how to relate the short (10- to 15-minute) exposures to the more usual hourly average monitoring data.

The effects of ambient air pollution on cardiac function in recent years has focused on PM, and several research groups in North America have exposed volunteers to concentrated ambient air particles and have reported effects on heart rate and heart rate variability, as discussed in Chapter 10. The first controlled study involving acute human exposure to sulfur dioxide involving cardiac function measurements was reported by Tunnicliffe et al. (*14*). It involved electrocardiogram recordings made for 12 normal and 12 asthmatic young adults. Exposures were of 1-hour duration, double blind, in random order, >2 weeks apart, and with clean air and 200 ppb (572 μg/m^3) sulfur dioxide. Spectral analyses

of R-R intervals were performed. The sulfur dioxide exposures were associated with statistically significant increases in high frequency (HF) and low frequency (LF) power in the normal subjects, and reductions in HF and LF of comparable magnitude in the asthmatic subjects. No pulmonary function changes or symptom frequency changes were observed in either group. These results suggest that sulfur dioxide exposures at concentrations frequently encountered during air pollution episodes can influence the autonomic nervous system. This may help in elucidating the mechanisms involved in the induction of bronchoconstriction, and the cardiovascular effects of ambient air pollution.

Epidemiological studies

Older epidemiological studies (up to about the mid-1980s) assessing the health effects of air pollution, including that caused by sulfur dioxide, have not been considered as providing reliable evidence for the independent effects of sulfur dioxide. Rather, they assessed the effects of the traditional pollutant mixture produced by fossil fuel combustion processes, which included PM and sulfur dioxide as primary pollutants plus secondary particles, including acid aerosols *(1)*.

Although epidemiological studies of air pollution exposure have the advantage of studying the populations of interest (including sensitive individuals) exposed at the usual ambient pollutant levels, and monitoring relevant outcomes (transient or irreversible), they have the drawback that they inevitably study exposure to a pollutant mixture. In recent years, however, more sophisticated statistical methodology has allowed the (at least) partial separation of the effects of individual pollutants via modelling. Furthermore, the large number of published studies is permitting an overall evaluation of the effects of sulfur dioxide in situations with varying pollutant mixes, and in particular with different levels of PM.

The main focus of the air pollution epidemiological studies in the past decade has been on the health effects of PM. However, numerous studies have also examined sulfur dioxide and other gaseous pollutants as potential confounders of the effects of PM. Thus, during the past decade a large number of risk estimates for sulfur dioxide have accumulated, providing a more comprehensive assessment of relative importance of the classical air pollutants. These observational studies have not resolved the issue of confounding between sulfur dioxide and PM or other pollutants, nor have they systematically examined the synergistic effects. Nevertheless, the accumulating risk estimates are still useful in assessing the potential adverse health impacts of sulfur dioxide. Generally, when multiple pollutants were evaluated, PM tended to be more strongly associated with mortality or morbidity outcomes than has sulfur dioxide, but there were a number of exceptions. The previous WHO guideline *(1)* covered literature up to 1996. In the following, we will discuss studies published in and after 1997. To minimize the potential influence of bias due to the software convergence issue that confounded analyses using the generalized additive model (GAM) (*15,16*), the

discussion that follows focuses on those studies that were unaffected or have been re-analysed.

In the following sections, short-term and long-term effects will be considered separately.

Short-term effects

In the past ten years, there have been nearly 200 mortality and morbidity time series studies that examined short-term impacts of PM, and about 60% of these studies also examined the impacts of sulfur dioxide. There have also been several multi-city studies of mortality and morbidity in Canada, Europe and the United States that also examined sulfur dioxide. These multi-city studies have advantages over a collection of single-city studies because they analyse data from many cities using consistent methodology and attempt to explain variations in the risk estimate using city characteristics (e.g. differences in weather, poverty, etc.). Therefore, this discussion focuses on the results from the multi-city studies.

Mortality studies

A series of studies from the Air Pollution and Health: A European Approach (APHEA) project examined mortality effects of air pollution in several cities. The APHEA 1 project *(17)* reported total non-accidental mortality risk estimates for sulfur dioxide and PM in 12 European cities, noting that the effects of these two pollutants were "mutually independent" and were stronger during the summer. The observed associations were stronger in western European cities than in central and eastern European cities (Table 1). The median levels of sulfur dioxide in these 12 cities ranged from 13 μg/m^3 (Bratislava) to 74 μg/m^3 (Cracow). An examination of cause-specific mortality in a subset of 10 of the above 12 cities found that estimated risks were larger for cardiovascular and respiratory categories than those for total non-accidental mortality *(18)*. Samoli et al. *(19,20)* applied an alternative model (a more flexible smoothing model to adjust for seasonal cycles) to the 12 cities data and also conducted subset analyses for moderate sulfur dioxide levels (<200 μg/m^3 and <150 μg/m^3). They found that both the alternative model and the restriction of the data to lower sulfur dioxide levels produced higher sulfur dioxide risk estimates, and reduced the contrast between western risk estimates and central and eastern risk estimates, although the pattern still remained.

The APHEA 2 project expanded the number of cities to 29 and added several more years of data, increasing the statistical power to explain possible city-to-city variations in air pollution mortality effects. However, the focus of its published mortality studies has been either PM indices *(26–28)*, nitrogen dioxide *(29)* or ozone *(30)*, and no mortality risk estimates have been reported for sulfur dioxide. The PM effects analyses reported that PM risk estimates were not affected by including sulfur dioxide in the models. The PM analyses, in their second stage

regressions, also found that nitrogen dioxide was an important effect modifier of PM (i.e. the cities with higher nitrogen dioxide levels showed larger PM risk estimates) in total mortality *(26,27)* and in elderly mortality *(28)*. While they did not report numerical data, the results imply that the difference in sulfur dioxide levels across cities did not alter the PM risk estimates. The median levels of sulfur dioxide in these 29 cities ranged from 4 μg/m^3 (Stockholm) to 49 μg/m^3 (Cracow).

A Spanish multi-city study (EMECAM) analysed short-term associations between mortality and sulfur dioxide and PM in 13 Spanish cities *(21)*. Note that this was a GAM study that has not been re-analysed. The study examined both 24-hour average and daily 1-hour maximum sulfur dioxide levels. The median levels of sulfur dioxide in these 13 cities ranged from 8 μg/m^3 (Seville) to 45 μg/m^3 (Oviedo). The results indicated that the estimated mortality risks for the 24-hour average sulfur dioxide were greatly reduced when two-pollutant models with PM were performed, but the estimates for 1-hour maximum sulfur dioxide were not attenuated by PM. The authors concluded that peak rather than daily average concentrations of sulfur dioxide were related to mortality.

The largest American multi-city mortality study, the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), while its main focus was on PM <10 μm in diameter (PM_{10}), also analysed sulfur dioxide and other gaseous pollutants in the 90 largest cities in the United States *(22,23)*. The mean levels of sulfur dioxide in these 90 cities ranged from 1 μg/m^3 (Riverside) to 39 μg/m^3 (Pittsburgh). In their re-analysis, Dominici et al. *(23)* noted that the results did not indicate significant associations for sulfur dioxide (or for nitrogen dioxide or carbon monoxide) with total mortality. These three pollutants were generally less strongly associated with mortality than PM_{10} or ozone. It should be noted that the combined estimates across cities for sulfur dioxide (and for nitrogen dioxide and carbon monoxide) were positive and significant at lag one day in single-pollutant models, and remained positive (though not significant because of larger confidence intervals) with additions of other pollutants. The estimated excess total mortality risk estimate per 50 μg/m^3 was 1.1% (95% PI 0.5–1.7)[1] smaller than those estimated in the APHEA 1 studies.

The results from the Canadian eight-cities study *(31)* (GAM-affected; re-analysed by Burnett and colleagues *(32)* but sulfur dioxide and other gaseous pollutants were not re-analysed) indicate that, while sulfur dioxide was significantly associated with total mortality in a single-pollutant model at lag one day, adding $PM_{2.5}$ reduced the sulfur dioxide risk estimates, and the association of sulfur dioxide with total mortality was generally the weakest among the pollutants. In

[1] The posterior interval (PI) used in Bayesian statistics can be interpreted similarly to the confidence interval. The 95% PI of 0.5–1.7 indicates that the posterior probability of the estimated excess total mortality risk per 50 μg/m^3 being in this range was 0.95.

the Canadian 11-cities study *(33)* (GAM-affected and not re-analysed), among the gaseous pollutants (PM was not analysed) the estimated excess mortality risk for sulfur dioxide at the mean level (~15 μg/m^3) of 1.4% was smaller than those for nitrogen dioxide (4.1%) or ozone (1.8%). The average levels of sulfur dioxide in these 11 cities ranged from 2 μg/m^3 to 29 μg/m^3. However, in the subsequent study of daily mortality in 12 Canadian cities *(34)*, when the average sulfur dioxide level was only 5 μg/m^3 (city-average range 0.9–9.6 μg/m^3), sulfur dioxide was significantly associated with daily mortality in a single-pollutant model and remained so in a multi-pollutant model with nitrogen dioxide. Also, it is noteworthy that the strength of the association with sulfur dioxide increased as the level of sulfur dioxide declined.

Stieb et al. *(24,25)* (re-analysis to evaluate the impact of GAM-affected studies) conducted meta-analyses of air pollutants by extracting results from 109 time series mortality studies conducted worldwide. For sulfur dioxide, there were 46 studies (29 non-GAM and 17 GAM) that reported single-pollutant estimates and 21 studies (10 non-GAM and 11 GAM) that reported estimates with co-pollutant(s) in the model. As shown in Table 1, the impacts of GAM and of including co-pollutants appear to be small. The average levels of sulfur dioxide in the studies reviewed in this meta-analysis ranged from 2 (San Bernardino, California) to 207 (Shenyan, China); they were generally low in American, Australian and Canadian cities, with some high-concentration areas in Europe (e.g. Erfurt, Germany), Central America (e.g. Mexico City) and Asia (e.g. Shenyang, China). However, the mortality estimates summarized did not show a clear relationship to the mean concentrations.

There are several single-city studies that need to be mentioned. Hoek et al. *(35,36*; re-analysis *37)* analysed associations between air pollution and total mortality as well as deaths from specific cardiovascular causes for the whole of the Netherlands. PM_{10}, black smoke, sulfur dioxide, ozone, nitrogen dioxide and carbon monoxide were analysed in single- and two-pollutant models in these studies. Essentially all the pollutants were significantly associated with total mortality in single-pollutant models. In two-pollutant models with sulfur dioxide and each of the PM indices (PM_{10}, black smoke, sulfate and nitrate), sulfur dioxide was more strongly associated with total mortality than these PM indices. The median level of sulfur dioxide in the Netherlands was 10 μg/m^3.

Wichmann et al. *(38)* (re-analysis by Stolzel et al. *(39)*) examined the mortality effects of fine and ultrafine particles in Erfurt, Germany. The numbers and mass concentrations of several size ranges of ultrafine particles, as well as $PM_{2.5}$, PM_{10}, TSP, sulfur dioxide, nitrogen dioxide and carbon monoxide, were analysed. Among the various PM indices, the strongest associations were found for the number concentrations in the 0.01–0.03-μm range and mass concentrations in the 0.01–2.5-μm range. Sulfur dioxide was associated with mortality more strongly than any of the fine or ultrafine particulate indices and other gaseous

Table 1. Estimated total (non-accidental) mortality expressed as percentage excess deaths (95% CI in parentheses) per 50-μg/m³ increase in sulfur dioxide reported in recent multi-city time series studies and meta-analyses

Study	Estimate	Comment
APHEA 1 *(17)*, 12 European cities	Western Europe: 2.9% (2.3–4.6) at the best lag between 0 and 3 days for each city Central and eastern Europe: 0.9% (0.2–1.5)	The effects of sulfur dioxide and PM were "mutually independent"
APHEA 1 *(19,20)*, 12 European cities, using natural splines rather than sine/ cosine to adjust for temporal trends	Western Europe: 2.6% (2.1–3.1) Central and eastern Europe: 0.7% (0.0–1.4)	Restricting data range below 150 or 200 μg/m³ increased sulfur dioxide risk estimates
EMECAM (*21*) (GAM study), 13 Spanish cities	2.5% (0.3–4.9), average of lag 0 and 1 days.	
NMMAPS *(22,23)*, 90 largest US cities	1.1% (0.5, 1.7) at lag 1 day	Adding co-pollutants reduced the estimate by ~20% and widened confidence bands
Stieb et al. meta-analyses *(24,25)*	Non-GAM: Single pollutant (29 studies): 1.7% (1.2–2.3) With co-pollutant(s) (10 studies): 1.6% (0.6–2.5) GAM: Single pollutant (17 studies): 2.0% (1.3–2.6) With co-pollutant(s) (11 studies): 1.6% (0.8–2.4)	

pollutants. In two-pollutant models with PM indices, sulfur dioxide remained more strongly associated with mortality than the PM indices. However, the authors stated that "the persistence of the sulfur dioxide effect was interpreted as artefact, because the sulfur dioxide concentration was much below levels at which effects are usually expected".

Wichmann et al. (*38*) noted that that the relative risk associated with sulfur dioxide was rising as the concentrations in Germany declined through the 1980s and 1990s, which they concluded was counterintuitive. They also noted that an examination by Buringh et al. *(40)* of a nine-year time series study of the whole Dutch population during a period of declining sulfur dioxide concentrations came to a similar conclusion. These analyses clearly indicate that caution must be exercised when considering whether low concentrations of sulfur dioxide

are a causal factor in the associations or merely a surrogate index for the causal factor.

Although the time series studies provide estimates of excess deaths from regression models, there remains a question as to whether a reduction in sulfur dioxide actually results in a reduction in deaths. A sudden change in regulation can provide a basis for treating the results as coming from an "intervention study". Such a situation occurred in Hong Kong, China, in July 1990 when a restriction was introduced over one weekend that required all power plants and road vehicles to use fuel oil with a sulfur content of not more than 0.5% by weight *(41)*. Unlike the other "intervention study" in Dublin *(2)*, where the ban on coal sales led to a 70% reduction in black smoke and 34% reduction in sulfur dioxide, in the Hong Kong case sulfur dioxide levels after the intervention declined by about 50% (from 44 to 21 μg/m^3) but PM_{10} levels did not change. In the study by Hedley et al. *(43)*, based on the Poisson regression of the monthly mortality data analysis, the average annual trend in death rate significantly declined after the intervention for all-cause (2.1%), respiratory (3.9%) and cardiovascular mortality (2.0%). It should also be noted that a time series mortality study in Hong Kong, China *(43)* suggested that sulfur dioxide was most consistently associated with mortality, whereas the association of PM_{10} with mortality was only marginal, further supporting the case for sulfur dioxide being more influential than PM in this locality. Thus, the Hong Kong case seems to suggest that a reduction in sulfur dioxide (or other pollutants associated with sulfur-rich fuel) leads to an immediate reduction in deaths, at least in the sulfur dioxide concentration range below 40 μg/m^3. It may be that the concentration–response relationship is steeper at low concentrations than at the higher concentrations more typical of those associated with coal smoke exposures. Samoli et al. *(29)* noted that restricting the APHEA project analyses to days with sulfur dioxide below 150 μg/m^3 increased the mortality coefficient, and that the increase occurred only in the formerly very highly polluted eastern European cities. As noted earlier for the Canadian daily mortality studies, the strength of the association with sulfur dioxide declines with declining concentration.

Meta-analyses of time series mortality studies performed in Asia between 1980 and June 2003, and meeting pre-selected criteria, were conducted by the International Scientific Oversight Committee of the Health Effects Institute *(44)*. For sulfur dioxide, there were 22 estimates from 12 cities for all-cause mortality, and 21 were positive. The Committee's tests for heterogeneity and publication bias were met, and two estimates of the size of the effect were made. The mean and 95% CI for fixed effects was 0.35% (0.26–0.45) and for random effects was 0.52% (0.30–0.74). These were quite close to the effects in APHEA 1*(45)*, which was 0.40% (0.3–0.5). For cardiovascular mortality, there were 11 estimates for 6 cities. All of them were positive, and the more precise estimates were about 2%.

Morbidity studies

The focus of acute morbidity studies in relation to air pollution in the past decade has also been on PM, but there have been several multi-city studies (mostly APHEA projects) that examined sulfur dioxide either as a potential confounder for PM or as a pollutant of primary interest. In the following we will summarize the results of the multi-city studies but also describe several important single-city studies.

APHEA 1 examined associations between emergency hospital admissions for asthma and black smoke, sulfur dioxide, nitrogen dioxide and ozone in four European cities *(45)*. Children under 15 years and adults aged 15–64 years were analysed. The median levels of sulfur dioxide in these cities ranged from 16 μg/ m^3 (Helsinki) to 41 μg/m^3 (Barcelona). Associations were found between hospital admissions for asthma and nitrogen dioxide in adults and sulfur dioxide in children. These associations were reported to be independent of black smoke. It should be noted that associations between sulfur dioxide and paediatric asthma admissions were seen in London and Paris but not in Helsinki.

Another APHEA 1 project examined associations between hospital admissions for chronic obstructive pulmonary disease (COPD) and sulfur dioxide, black smoke, TSP, nitrogen dioxide and ozone in six European cities *(46)*. The median levels of sulfur dioxide in these cities ranged from 21 μg/m^3 (Amsterdam) to 53 μg/m^3 (Milan). In the combined estimates across cities, sulfur dioxide was not as strongly associated with COPD admissions as other pollutants, but this appeared to be at least partly due to the larger heterogeneity of sulfur dioxide estimates across cities compared to those of other pollutants – the sulfur dioxide risk estimates were significantly positive in Paris, Milan and Barcelona but negative in Amsterdam and Rotterdam. Other pollutants showed more consistent results across cities, giving overall statistically significant estimates. Their analysis by season found that associations between sulfur dioxide and admissions for COPD were stronger in warm seasons.

Spix et al. *(47)* summarized associations between air pollution and hospital admissions for respiratory diseases by age (15–64 years and 65+ years) in five west European cities as part of the APHEA 1 project. The median levels of sulfur dioxide in these cities ranged from 21 μg/m^3 (Amsterdam) to 66 μg/m^3 (Milan). In this study, the most consistent associations for both adult and elderly respiratory admissions were found with ozone. The authors concluded that: "no consistent evidence of an influence on respiratory admissions was found" for sulfur dioxide. However, they also noted that the heterogeneity of estimated sulfur dioxide effects across cities was best explained by the number of stations that provided data (i.e. larger effects for cities with more monitoring stations). Thus, the exposure estimation error associated with sulfur dioxide may have affected the results. The combined effect estimate for elderly admissions was positive and significant.

In the APHEA 2 project, Atkinson et al. *(48)* (re-analysis of GAM *(49)*) investigated acute effects of PM on respiratory admissions in eight European cities, but sulfur dioxide was examined only for its influence on PM risk estimates in two-pollutant models and the risk estimates for sulfur dioxide were not reported. Asthma (in 0–14- and 15–64-year-olds), COPD and all-respiratory causes (65+ years) were examined. PM (especially PM_{10}) was associated with these outcomes, and ozone was suggested as a potential modifier of the PM effects. The inclusion of sulfur dioxide in the models modified (reduced) PM_{10}–asthma associations only in the 0–14-year age group. Sunyer et al. *(50)* (a GAM study) specifically examined the effects of sulfur dioxide on respiratory admissions in the seven APHEA 2 cities. The median levels of sulfur dioxide in these cities ranged from 5 μg/m^3 (Stockholm) to 21 μg/m^3 (London). The respiratory categories examined were the same as those analysed by Atkinson et al. *(45)*. Sulfur dioxide was associated with asthma admissions in children, but not with other respiratory diseases in other age groups. The authors also noted that the sulfur dioxide risk estimates were sensitive to the inclusion of PM_{10} or carbon monoxide in the models. Owing to relatively high correlations among these pollutants, the issue of potential confounding could not be resolved.

Le Tertre et al. *(51)* (re-analysis *(52)*) examined the association between PM (PM_{10} and black smoke) and hospital admissions for cardiovascular causes in eight European cities as part of the APHEA 2 project. Hospital admissions for total cardiovascular diseases, cardiovascular diseases in those aged 65+, ischaemic heart disease (IHD) in those aged 0–64, IHD in those aged 65+ and stroke in those aged 65+ were analysed. They did not specifically estimate sulfur dioxide effects, but examined the sensitivity of PM risk estimates when sulfur dioxide and other gaseous pollutants were added. Adding sulfur dioxide in the regression models did not affect PM risk estimates, but adding carbon monoxide and especially nitrogen dioxide greatly reduced PM risk estimates. The authors concluded that the primary effect was probably attributable to diesel exhaust. Sunyer et al. *(53)* (a GAM analysis) analysed the same outcomes as those studied by Le Tertre et al. *(52)* and provided combined sulfur dioxide risk estimates across seven cities (Barcelona excluded). Single pollutant models resulted in positive and significant sulfur dioxide risk estimates for all of the cardiac outcomes except stroke. However, these estimates were reduced when carbon monoxide, nitrogen dioxide, black smoke or PM_{10} were included in the models (except for IHD admissions for those aged under 65 years. The authors noted that sulfur dioxide could be a surrogate of urban pollution mixtures that in some cases is more strongly associated with cardiovascular hospital admissions than particles.

The NMMAP analysis of elderly respiratory and cardiovascular hospital admissions from 14 American cities focused on PM_{10} effects. Sulfur dioxide was analysed only to examine its influence on PM_{10} risk estimates in the second-

stage regression *(22)* (re-analysis by Schwartz et al. *(54)*). The authors concluded that there was little evidence of PM_{10} effects confounded by sulfur dioxide.

There were several other, smaller-scale studies suggesting roles for sulfur dioxide in respiratory and cardiovascular outcomes. A six-month follow-up of 84 asthmatic children in Paris (mean sulfur dioxide = 22 μg/m^3) found an association between air pollution and increased asthma attacks and symptoms in mildly asthmatic children *(55)*. The strongest association was found for the risk of asthma attacks and sulfur dioxide on the same day. A comparison of air pollution effects on respiratory and cardiovascular hospital admissions in Hong Kong (mean sulfur dioxide = 15 μg/m^3) and London (mean sulfur dioxide = 21 μg/m^3) found that sulfur dioxide was associated with cardiac admissions after adjusting for other pollutants *(56)* (a GAM analysis).

The Hong Kong "intervention" event described earlier also provided an opportunity to investigate health end-points other than mortality. Wong et al. *(57)* compared the effects of the intervention on bronchial responsiveness in primary school children living in two districts (polluted vs less polluted) in Hong Kong. Bronchial hyperreactivity and bronchial reactivity slope were used to estimate responses to a histamine challenge. They found a greater decline in both parameters in the polluted than in the less polluted district. The results suggest that the reduction in sulfur dioxide level was associated with a reduction in bronchial hyperresponsiveness in schoolchildren.

In an analysis of morbidity after the step-change in ambient sulfur dioxide concentration in Hong Kong, Wong et al. *(57)* examined associations of sulfur dioxide, nitrogen dioxide, PM_{10} and ozone air pollution with hospital admissions for respiratory diseases, cardiac diseases, IHD and asthma in both Hong Kong and London, when both cities had similar sulfur dioxide concentrations. For sulfur dioxide concentrations in the 5–40-μg/m^3 range in Hong Kong, there were non-threshold and nearly linear relationships between sulfur dioxide on the one hand and cardiac and respiratory admissions on the other, but no trends for IHD or asthma. For London, there were non-threshold and nearly linear relationships between sulfur dioxide on the one hand and cardiac disease and IHD on the other, but not for respiratory disease or asthma. It is noteworthy that there was essentially the same association between sulfur dioxide and cardiac disease admissions for both of these very large cities, despite their differences in climate and ethnicity. Some biological plausibility for an effect of sulfur dioxide on cardiac admissions may lie in the report of Tunnicliffe et al. *(14)* indicating significant heart rate variability changes in asthmatic volunteers exposed to sulfur dioxide for one hour at 572 μg/m^3. Their intake for that one hour would be the same as for a 24-hour exposure to 24 μg/m^3.

The International Scientific Oversight Committee of the Health Effects Institute *(44)* conducted a meta-analysis of time series studies on respiratory hospital admissions performed in Asia between 1980 and June 2003, and that met

pre-selected criteria. For sulfur dioxide, there were 14 studies from China (Hong Kong) and 4 from the Republic of Korea, with 10 showing positive associations. For cardiovascular hospital admissions, all of the studies were from Hong Kong and were positive.

Long-term effects

Earlier studies on the chronic effects of air pollutants relied on cross-sectional comparisons that could be subject to ecological confounding. More recent studies often involve investigations of large cohorts for which detailed individual-level information is collected to adjust for confounding. The air pollution exposure estimates in these studies are still "ecological" in the sense that all the subjects in a community are assigned the same community average air pollution level, but the ability to adjust for potential confounders (smoking, diet, body mass index, occupational exposure, etc.) on the individual level is a major advantage over purely ecological studies. Hence, this type of study is called "semi-individual" *(58)*. Since these are prospective cohort studies they require extended periods and resources, and thus there have not been many such studies. Since the previous WHO guidelines *(1)* were published, several mortality studies have been conducted, some of which are extensions of those discussed in the previous review.

Mortality studies

Krewski et al. *(59)* re-analysed two large American cohort studies, the Harvard Six Cities study *(60)* and the American Cancer Society (ACS) data *(61)*. Their replication analyses confirmed the original investigators' findings of PM effects, and their additional analyses of the ACS data reported several interesting observations. Of the gaseous pollutants examined (sulfur dioxide, nitrogen dioxide, ozone and carbon monoxide), only sulfur dioxide showed positive and significant associations with all-cause mortality. This association appeared to be robust against adjustment for other variables, including fine particles and sulfate. The risk estimates for fine particles and sulfate were reduced when sulfur dioxide was jointly included in the models. These findings are not too surprising in that the high sulfur dioxide areas overlap the areas of high sulfate and fine particles in these data, and therefore "independent" mortality associations of these variables may be difficult to infer from statistical analyses alone. However, the findings at least suggest an effect of air pollution sources that emit sulfur dioxide.

There have been two updated analyses of the ACS cohorts. In the analysis by Pope et al. *(62)*, the follow-up data of approximately half a million subjects during 1982–1998 were linked to fine particle, sulfate and gaseous pollutant data. The mean annual sulfur dioxide levels for the 1980 and 1982–1998 periods were 27 (standard deviation = 13) and 18 (standard deviation = 8.0) $\mu g/m^3$, respectively. Fine particles were associated with deaths due to all, cardiopulmonary and lung cancer causes. Sulfur dioxide was the only gaseous pollutant associated with

mortality. This was consistent with the extended analysis of the original ACS data (1982–1988 follow-up period) carried out by Krewski et al. *(59)*. The 2004 study by Pope et al. *(63)* analysed more specific cardiovascular causes from the 1982–1998 follow-up data and found associations between $PM_{2.5}$ and IHD, dysrhythmias, heart failure and cardiac arrest, but sulfur dioxide and other pollutants were not examined.

Another large American cohort study, the Adventist Health Study of Smog (AHSMOG), followed a cohort of over 6000 non-smoking Californian Seventh Day Adventists from 1977. The AHSMOG study *(64)* analysed the 1977–1992 follow-up period. PM_{10} was associated with non-malignant respiratory disease as well as with lung cancer in males. Sulfur dioxide was associated with lung cancer for both males and females. However, the number of cases of lung cancer in this study was relatively small (18 for males and 12 for female) and thus interpretation of these results requires caution *(38)*.

Lung function changes

These effects have generally been assessed using measurements of ventilatory capacity such as $FEV_{0.75}$, FEV_1, forced vital capacity (FVC) and peak expiratory flow (PEF) *(3)*. Small effects on lung function have been observed at low levels of exposure (<300 μg/m^3) but it is difficult to separate the independent effects of sulfur dioxide *(3)*.

Evaluation

Exposure evaluation

In much of Europe and North America, concentrations of sulfur dioxide in urban areas have declined substantially in recent years as a result of controls on emissions and changes in fuel use. Annual mean concentrations in such areas are now mainly in the range 12–45 μg/m^3 (0.004–0.015 ppm), with daily means seldom more than 70 μg/m^3 (0.025 ppm). In large cities where coal is still widely used for domestic heating or cooking, however, or where there are poorly controlled industrial sources, concentrations may be 5–10 times those values. Peak concentrations over shorter averaging periods, of the order of 10 minutes, can reach 1000–2000 μg/m^3 (0.35–0.70 ppm) in some circumstances, such as the grounding of plumes from major point sources or during peak dispersion conditions in urban areas with multiple sources.

Health risk evaluation

Short-term exposure (less than 24 hours)

The most direct information on the acute effects of sulfur dioxide comes from controlled chamber experiments on volunteers. Most of these studies have been for exposure periods ranging from a few minutes up to one hour. The exact

duration is not critical, however, because responses occur very rapidly, within the first few minutes from commencement of inhalation; continuing the exposure further does not increase the effects. The effects observed include reductions in FEV_1 or other indices of ventilatory capacity, increases in specific airway resistance, and symptoms such as wheezing or shortness of breath. Such effects are enhanced by exercise, which increases the volume of air inspired, thereby allowing sulfur dioxide to penetrate further into the respiratory tract. An acute effect of short-term exposure at rest to 0.2 ppm sulfur dioxide is a change in heart rate variability, in which normal young adults responded with small but statistically significant increases in both high and low frequency power, while asthmatic subjects responded with decreases in these parameters of comparable magnitude.

A wide range of sensitivity has been demonstrated, both among normal individuals and among those with asthma, who form the most sensitive group for pulmonary function changes. Continuous exposure–response relationships, without any clearly defined threshold, are evident. To develop a guideline value, the minimum concentrations associated with adverse effects in the most extreme circumstances (i.e. with asthmatic patients exercising in chambers) have been considered. An example of an exposure–response relationship for such subjects was given by Linn et al. *(13)* and was expressed in terms of reductions in FEV_1 after a 15-minute exposure. Only small changes, not regarded as of clinical significance, were seen at 572 $\mu g/m^3$ (0.2 ppm); reductions representing about 10% of baseline FEV_1 occurred at about 1144 $\mu g/m^3$ (0.4 ppm); and reductions of about 15% occurred at about 1716 $\mu g/m^3$ (0.6 ppm). The response was not greatly influenced by the severity of asthma. These findings are consistent with those reported from other exposure studies. In one early series, however, a small change in airway resistance was reported in two of the asthmatic patients at 286 $\mu g/m^3$ (0.1 ppm).

Exposure over a 24-hour period

Observational time series studies have reported numerous mortality and morbidity risk estimates for sulfur dioxide in the past decade. The consistency of the association of sulfur dioxide with health outcomes appears to be less than that for PM. As mentioned above, however, there are exceptions and the magnitude of estimated risks were often comparable to that of PM. Interestingly, many of the researchers, in their discussions when sulfur dioxide associations were found, did not often interpret these sulfur dioxide associations with mortality or morbidity as causal but rather as "artefact", and suggested that sulfur dioxide was acting as a "surrogate" for a source type. The reasoning offered for the sulfur dioxide levels being "too low" to be causal was based on prior knowledge. This situation highlights a limitation of the observational studies, the "surrogate" interpretation, i.e. that sulfur dioxide represents a source type (e.g. coal-fired power plant), or a mixture that can affect health through a co-pollutant (e.g. PM), or through pollutants that it is converted into (i.e. sulfuric acid and sulfates). Yet another

interpretation is that PM becomes more toxic when sulfur dioxide coexists and gets adsorbed onto PM surfaces. Reanalysis of Philadelphia time series data some years ago found some indication that the proportional increment in daily mortality associated with TSP was greater at higher levels of sulfur dioxide *(65)*. In any case, the current observational studies were not designed to resolve these issues. The Hong Kong intervention studies do suggest that reducing the use of sulfur-rich fuels leads to reductions in adverse health effects.

In the past, exacerbation of symptoms among panels of selected sensitive patients occurred consistently when the concentration of sulfur dioxide exceeded 250 μg/m^3 (0.087 ppm) in the presence of PM. Such findings were related mainly to situations in which emissions from the inefficient burning of coal in domestic appliances was the main contributor to the pollution complex. More recent studies, involving the mixed stationary and vehicular sources that now dominate, have consistently demonstrated effects on daily mortality (total, cardiovascular and respiratory) and hospital emergency admissions for total respiratory causes and COPD at much lower levels of exposure (mean daily levels below 50 μg/m^3). The Hong Kong "intervention" study indicated significant health benefits in reducing sulfur dioxide from a daily average of 44 μg/m^3 to 21 μg/m^3. As with ozone and PM, no obvious threshold levels have so far been identified in these population-based studies.

Long-term exposure

A similar situation arises in respect of effects of long-term exposures, expressed as annual averages. Earlier assessments examined findings on the prevalence of respiratory symptoms, respiratory illness frequencies or differences in lung function values in localities with contrasting concentrations of sulfur dioxide and PM, largely in the coal-burning era. The lowest observed adverse effect level (LOAEL) of sulfur dioxide was judged to be 100 μg/m^3 (0.035 ppm) annual average together with PM. The more recent studies related to the changed urban mixture have shown associations between ambient levels of sulfur dioxide and adverse effects at concentrations well below this level (18–27 μg/m^3), but one major difficulty in interpretation is that long-term effects are liable to be affected not only by current conditions. Another is the qualitatively and quantitatively different pollution of earlier years. Cohort studies of differences in annual mortality between areas with contrasting pollution levels indicate that there is a closer association with PM, sulfur dioxide and sulfate aerosol than with other measured air pollutants.

Guidelines

Short-term exposures

Controlled studies with exercising asthmatics indicate that some of them experience changes in pulmonary function and respiratory symptoms after periods of

exposure as short as 10 minutes. Based on this evidence, it is recommended that a value of 500 μg/m^3 should not be exceeded over averaging periods of 10 minutes. Because exposure to sharp peaks depends on the nature of local sources and meteorological conditions, no single factor can be applied to this value in order to estimate corresponding guideline values over somewhat longer periods, such as an hour.

Exposure over a 24-hour period and long-term exposure

Day-to-day changes in mortality, morbidity or lung function related to 24-hour average concentrations of sulfur dioxide are necessarily based on epidemiological studies in which people are in general exposed to a mixture of pollutants, with little basis for separating the contributions of each to the effects. This is the reason that guideline values for sulfur dioxide before 1987 were linked with corresponding values for PM. This approach led to a guideline value of 125 μg/m^3 as a 24-hour average, after applying an uncertainty factor of 2 to the LOAEL. In the 2000 revision *(1)*, it was noted that recent epidemiological studies showed separate and independent adverse public health effects for PM and sulfur dioxide, and this led to a separate WHO air quality guideline for sulfur dioxide of 125 μg/m^3 as a 24-hour average. More recent evidence, beginning with the Hong Kong study *(41)* of a major reduction in sulfur content in fuels over a very short period of time, shows an associated substantial reduction in health effects (childhood respiratory disease and all-age mortality outcomes). In time series studies on hospital admissions for cardiac disease, there is no evidence of a concentration threshold within the range of 5–40 μg/m^3 in both Hong Kong and London *(56)*. Daily sulfur dioxide was significantly associated with daily mortality in 12 Canadian cities with an average concentration of only 5 μg/m^3 *(34)*. If there were a sulfur dioxide threshold for either the study of daily mortality by Burnett et al. *(34)* or the annual mortality study of Pope et al. *(62)*, they would have to be very low. For the significant associations in the ACS cohort for 1982–1998 in 126 United States metropolitan areas, the mean sulfur dioxide was 18 μg/m^3 *(62)*.

Nevertheless, there is still considerable uncertainty as to whether sulfur dioxide is the pollutant responsible for the observed adverse effects or, rather, a surrogate for ultrafine particles or some other correlated substance. In Germany *(38)* and the Netherlands *(40)*, for example, a strong reduction in sulfur dioxide concentrations occurred over a decade. Although mortality also decreased with time, the association of sulfur dioxide and mortality was judged not to be causal and was attributed to a similar time trend of a different pollutant (PM). In consideration of (*a*) the uncertainty of sulfur dioxide in causality, (*b*) the practical difficulty of reaching levels that are certain to be associated with no effects and (*c*) the need to provide greater degrees of protection than those provided by the guidelines published in 2000, and assuming that reduction in exposure to a causal and correlated substance is achieved by reducing sulfur dioxide concentrations,

Table 2. Sulfur dioxide air quality guidelines and interim targets to be achieved in improving air quality

	24-hour average	10-minute average
WHO interim target 1 (IT-1) (2000 guideline level)	125 μg/m^3	–
WHO interim target 2 (IT-2)	50 μg/m^3 Intermediate goal based on controlling either (*a*) motor vehicle (*b*) industrial emissions and/or (*c*) power production; this would be a reasonable and feasible goal to be achieved within a few years for some developing countries and lead to significant health improvements that would justify further improvements (such as aiming for the guideline).	–
WHO air quality guidelines	20 μg/m^3	500 μg/m^3

there is a basis for revising the 24-hour guideline for sulfur dioxide downwards, adopting a prudent precautionary approach. Since the recommended 24-hour guideline may be quite difficult for some countries to achieve in the short term, we suggest a stepped approach using interim goals, as shown in Table 2.

An annual guideline is not needed, since compliance with the 24-hour level will assure low levels for the annual average.

For instance, a country could move towards guideline compliance by controlling emissions from one major source at a time, selecting among motor vehicle sources, industrial sources and power sources for the greatest effect on sulfur dioxide at the lowest cost, and monitoring public health and sulfur dioxide levels for health effect gains. Demonstrating health benefits will provide an incentive to introduce controls for the next major source category.

These recommended guideline values for sulfur dioxide are not linked with guidelines for particles.

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Part 3

Annexes

Annex 1

Pathogenesis of ozone-dependent injury

Ozone-dependent injury is the result of a series of complex events, such as direct oxidation of cell constituents, inflammation and neural reflexes. At the same time, adaptive and protective mechanisms are activated. These events occur simultaneously, and the interaction among them determines the magnitude of the resulting damage. For didactic purposes, the series of pathophysiological events triggered by ozone exposure will be presented separately.

Direct oxidation of cellular constituents

Ozone is a potent oxidant and may induce either direct or indirect oxidative stress (through inflammatory reactions) to respiratory epithelia. Direct oxidative stress occurs when ozone contacts cells located in areas not covered by ELF, or in cells that may protrude above ELF, such as macrophages. Oxidative damage is mediated by a series of electron transfers initiated by the high electron affinity of oxidant chemical species. The unstable electron configuration of ozone begins a series of redox reactions with adjacent molecules such as proteins, lipids, carbohydrates and DNA. The interaction between lipids and ozone may trigger an autocatalytic process that impairs the integrity of cell and organelle membranes. Oxidation of proteins may promote the formation of protein–protein cross-linkages and protein fragmentation, augmenting the rate of protein degradation within the cell. Abnormal protein folding due to protein cross-linkings, tending to accumulate in endoplasmic reticulum, may trigger the unfolded-protein response *(1)* that plays a significant role in certain degenerative diseases such as Alzheimer and Parkinson. Interestingly, Calderón-Garcidueñas et al. *(2)* recently reported Alzheimer-like pathology in individuals living in areas with high levels of air pollution.

Products of the oxidation of lung surfactant by ozone induce apoptosis of alveolar epithelial cells in vitro through the activation of the mitochondrial pathway *(3)*, thus changing the turnover of respiratory epithelium without eliciting significant inflammation. Low levels of oxidants promote acute abnormalities of ciliated epithelium, characterized by ciliary fusion, impairment of ciliary transport and augmented trans-epithelial permeability *(4)*, which may take hours to days to recover *(5–7)*. Although the entire respiratory tract may be injured by ozone, cells at the extremes of the respiratory pathway – basal turbinates *(8–12)* and terminal bronchioli and proximal airway passages *(13–19)* – seem to be the

most susceptible. Short-term exposure to ozone induces necrosis of type 2 alveolar cells in vitro *(20)* as well as in vivo *(21)*. The topographical distribution of respiratory lesions is probably the result of the balance between the rate of local reactive absorption of ozone, the time of interaction between ozone and the underlying constituents of the airways, and cell structural and antioxidant defences along the different segments of the respiratory tract *(19)*.

In addition to cell damage, oxidation of nuclear and mitochondrial DNA may lead to point mutations or DNA breaks, processes involved in the pathogenesis of neoplasia and ageing *(22,23)*. Ozone induces DNA strand breaks in animal studies *(24,25)* as well as in vitro *(26)* and in humans *(27,28)*. Ozone-caused cleavages in the deoxyribose phosphate backbone of double-stranded DNA are partially mediated by hydroxyl radicals. Ozone also induces base substitutions, essentially located at G : Cs *(29)* and transversion at the locus of the *hprt* gene *(30)*. Although animal studies on lung carcinogenicity of ozone are not conclusive *(17,19)*, there is some evidence that ozone is associated with increased incidence of tumours of the upper respiratory tract in humans *(31)*.

Induction of respiratory and systemic inflammation

The previous section showed that ozone inhalation promotes oxidation of several substrates in the respiratory tract, such as ELF, cell membranes and DNA. Non-programmed cell death triggers an inflammatory process, which may amplify the direct oxidative damage. In fact, inflammation represents the main pathogenetic mechanism of ozone-dependent health effects. Inhalation studies in healthy humans have demonstrated that exposure to ambient levels of ozone elicits a significant inflammatory reaction composed of cellular influx and release of inflammatory mediators and cytokines *(32)*.

The association between ozone and pulmonary inflammation seems to be dose-dependent. By pooling the results of a series of studies relating ozone to changes in neutrophil counts in bronchoalveolar lavage (BAL), Mudway & Kelly *(33)* obtained a linear association between dose (expressed as mg/m^2 body surface area) and neutrophilia in BAL fluid samples. Since inflammation is the main component of ozone toxicity, there is a large body of literature on local and systemic inflammation after ozone exposure, encompassing animal inhalation studies, controlled human exposures and human field studies. There is also a wide variation of dose, time and sequence (single vs multiple exposures) presented in the available literature, providing a good picture about the minimum toxic dose, time course, mechanisms of inflammation and adaptation, and the consequences of airway remodelling after acute and prolonged exposures. Nevertheless, the mechanisms of ozone injury should be approached with some degree of systematization, which necessarily implies some degree of artificiality since the different processes – injury, inflammation, adaptation and remodelling – are interconnected.

Thus, the following section is divided as follows: (*a*) production of inflammatory mediators; (*b*) time course of inflammation induced by ozone; (*c*) mechanisms of ozone tolerance; and (*d*) airway and pulmonary parenchyma remodelling. Particular emphasis is placed on those exposure protocols near ambient levels of ozone, in order to provide the basis for understanding the health effects on humans depicted by epidemiological studies.

Production of inflammatory mediators

Local generation of bioactive substances

Interaction of ozone with components of ELF may generate chemical species capable of triggering inflammation and cell damage *(34)*. Despite the presence in ELF of water-soluble antioxidants such as ascorbic acid, glutathione and uric acid *(35–37)*, exposure to even ambient levels of ozone leads to the production of lipid ozonation products such as aldehydes *(34,38)*. DNA-reactive aldehydes from lipid peroxidation may form adducts with DNA, potentially deregulate cellular homeostasis and drive normal cells to malignancy *(39)*, suggesting that ozone may play a role in the development of respiratory tract neoplasms.

Influx of plasma proteins

Plasma proteins belonging to the interrelated complement, clotting and kinin systems influence and mediate inflammation. The demonstration of plasma proteins in BAL samples occurs soon after ozone exposure; tissue factor and clotting factor VII increased after only one hour in BAL samples from healthy people exposed to 0.8 mg/m^3 ozone for two hours during intermittent heavy exercise *(40)*. Thus the activation of plasma systems is expected to participate in the inflammatory reaction caused by ozone. In fact, complement-depleted mice exposed to 4 μg/m^3 ozone for three hours showed reduced airway hyperresponsiveness and neutrophilic inflammation compared to controls *(41)*. In addition, complement was shown to enhance the removal of necrotic cells after ozone exposure *(42)*.

Release of preformed inflammatory mediators

Mast cells, basophils and platelets contain preformed inflammatory mediators such as histamine and serotonin, mediators that acutely induce vascular and cellular inflammatory responses and play a significant role in acute and chronic inflammation triggered by ozone inhalation. In addition, pulmonary C fibres contain inflammatory neuropeptides that can be released after ozone exposure.

In vitro exposure to 0.12 mg/m^3 ozone for 24 hours induces mast cell degranulation in human nasal mucosa *(43)*. Short-term exposure to low ozone levels (0.8 mg/m^3 for two hours) induced degranulation of mast cells in normal volunteers as detected by nasal lavage *(44)*, the same finding being demonstrated in sheep *(45)* and mice *(46)*. Inflammation induced by a single short exposure to ozone was less intense in genetically mast-cell-deficient (WBB6F1-W/Wv) mice than

in mast-cell-sufficient congenic mice *(47,48)*. After exposure to ambient levels of ozone for up to 90 days, mast-cell-sufficient mice had significantly greater increases in lung macrophages, epithelial cells and polymorphonuclear leukocytes, as well as impaired reversibility of inflammatory lesions, than mast-cell-deficient mice *(49,50)*. These findings clearly indicate that cell-stored inflammatory mediators play a significant role in acute and chronic effects of ozone.

Ozone stimulates airway sensory nerves, firing reflexes *(51)* or releasing tachykinins *(52)*. In the airways, release of tachykinins such as substance P from sensory nerves can stimulate mucus secretion, bronchoconstriction and increases in the permeability of lung microcirculation, pathological events commonly described as consequent to both acute and chronic exposure to ozone. In addition to their direct action on airway smooth muscle, epithelial cells and microcirculation, tachykinins have several proinflammatory properties, including the activation, priming and migration of inflammatory cells and causing mast cell degranulation *(53–57)*. Neuropeptides may play different roles in the environment, having an enhancing or protective effect on lung inflammation after ozone inhalation. Animal studies designed to assess the role of sensory nerves in determining ozone-induced inflammation reported conflicting results depending on the species. Guinea-pigs treated with capsaicin to reduce the amount of tachykinin-containing sensory nerves showed attenuated inflammation when exposed to ozone in comparison with controls, indicating that sensory nerves contribute to ozone-induced inflammation *(58,59)*. When exposed to ozone, genetically manipulated mice with hyperinnervation of sensory nerves in the airways showed significantly more severe inflammation (expressed in terms of cytokines or inflammatory cell counts in BAL) compared with animals with diminished airway innervation *(60)*. Krishna et al. *(61–63)* demonstrated that human normal volunteers, when exposed to 0.4 mg/m^3 ozone for two hours, had a significant release of substance P from airway sensory nerves and that the amount released was inversely correlated with decrements in forced expiratory flow (FEF). There was a positive association with neutrophils in BAL, indicating that substance P, stored in airway sensory nerves, contributes to bronchoconstriction and inflammatory cell recruitment in normal humans exposed to ozone. These results indicate that the release of tachykinins by airway sensory nerves most probably enhances the inflammatory response elicited by ozone inhalation.

Synthesis of arachidonic acid metabolites

Lysis of cell membranes promotes the metabolism of membrane phospholipids by phospholipases (e.g. phospholipase A2), resulting in the formation of arachidonic acid. Arachidonic acid is a 20-carbon polyunsaturated fatty acid, which does not occur free in the cell but is present in membrane phospholipids, being released from them by the action of phospholipases. Phospholipases may be activated by a variety of stimuli, including components of the complement

system, an increase in the intracellular levels of Ca^{2+} and the action of various kinases. The reaction between ozone and unsaturated fatty acids in ELF and cell membranes generates a cascade of lipid ozonation products that mediate the activation of phospholipases and the release of arachidonic acid in the pulmonary environment *(64)*. Arachidonic acid may be metabolized by two main pathways: the cyclooxygenase pathway (forming prostaglandins and thromboxanes) and the lypoxygenase pathway (producing leukotrienes and lipoxins). These mediators act on the target cells through G-protein coupled receptors and literally participate in all steps of the inflammatory process. For instance, vasoconstriction and bronchoconstriction are results of thromboxane A2 and leukotrienes C4, D4 and E4. Some prostaglandins (PGI2, PGE1, PGE2, PGD2 and prostacyclin) have a relaxing effect on smooth muscle. Leukotrienes C4, D4 and E4 induce a marked increase in vascular and epithelial permeability, whereas leukotriene B4, 5-hydroxyeicosatetraenoic acid and lipoxins markedly stimulate chemotaxis and leukocyte adhesion.

There is growing evidence for the participation of metabolites of arachidonic acid in the inflammatory process induced by ozone *(32,65)*. In vitro exposure of bovine tracheal epithelium *(66)* and human bronchial cells *(67)* to ozone increases the metabolism of arachidonic acid through cyclooxygenase and lipoxygenase pathways in concentrations as low as 0.2 mg/m^3. Schierhorn et al. *(68)* reported that human nasal epithelium, when exposed to ozone in vitro, exhibited increases of both cyclooxygenase and lipoxygenase products. Inhalation of 0.8 mg/m^3 ozone for two hours significantly increased the concentration of 8-isoprostane, a prostaglandin-F(2 alpha) isomer that is formed in vivo by free-radical-catalysed peroxidation of arachidonic acid in healthy persons *(69)*. Administration of the non-steroidal anti-inflammatory drug ibuprofen (an inhibitor of cyclooxygenase) blunted the decrement of pulmonary function induced by the inhalation of ozone (0.8 mg/m^3 for two hours) in normal volunteers without affecting the numbers of neutrophils in BAL samples *(70)*.

In rats exposed to near-lifetime ozone, Szarek & Valentovic *(71)* reported that the cyclooxygenase pathway of the arachidonic acid cascade appears to be the most important. Coffey et al. *(72)* reported, however, an increase in BAL fluid of leukotriene (LT) C4 (8-fold) and to a lesser extent LTB4 (1.5-fold) levels in healthy volunteers exposed to 0.8 mg/m^3 ozone for two hours, suggesting that the lipoxygenase pathway may be more important after ozone inhalation than the cyclooxygenase pathway. Interestingly, cyclooxygenase metabolites may play a different role in the ozone-induced decline in pulmonary function, depending on the pre-exposure condition of the lungs. Alexis et al. *(73)* reported that cyclooxygenase metabolites contribute to restrictive-type changes in normal people (probably because of activation of nociceptive receptors in the lungs) and obstructive-type changes in small airways in asthmatics, an event mostly dependent on inflammation.

Synthesis of cytokines and chemokines

Cytokines are proteins produced by lymphocytes, macrophages, endothelium, epithelium and connective tissue that modulate the immune system as well as acute and chronic inflammation. Chemokines are small proteins (8–10 kD) secreted by macrophages, endothelial cells and epithelial cells that stimulate leukocyte recruitment and migration in tissues. There is solid evidence that this inflammatory pathway, dependent on the activation of inflammatory and pulmonary cells after ozone injury, plays a pivotal role in ozone-dependent injury.

Human nasal epithelium exposed to ozone (0.2 mg/m^3) in vitro for 24 hours showed a significant increase in (IL)-1 beta, IL-6, IL-8 tumour necrosis factor-alpha, such increase being more pronounced if tissue was sampled from patients with atopy *(43)*. The same findings were also described for human airway cells *(74)*, with greater response in cells harvested from asthmatics *(75,76)*. Healthy volunteers showed increased amounts of cytokines in BAL shortly after ozone exposure *(40)*. Acute exposure of mice to ozone promoted a significant increase in mRNA of the chemokines MCP-1 and MIP-2, followed by a corresponding increase in neutrophil count in BAL through activation of nuclear factor-kappa B (NFκB) transcription factor *(77,78)*, which enhances the synthesis of a wide range of proinflammatory genes. Activation of NFκB is dependent on Toll-like receptors, a family of membrane proteins with sequence homology with *Drosophila* Toll proteins *(79)*. In mice, the neutrophil chemokines KC and macrophage inflammatory protein-2 (MIP-2) are expressed in the lungs following ozone exposure and animals with deficiency in CXCR2, the receptor for these chemokines, show reduced inflammation and airway obstruction after ozone challenge *(80)*. Administration of interleukin-1 receptor antagonist attenuates airway hyperresponsiveness following exposure to ozone in mice *(41)*, and interleukin-6-deficient mice have decreased inflammatory response to ozone but show no effect on airway hyperresponsiveness *(81)*. Knockout mice deficient in tumour necrosis factor receptor had significantly less ozone-induced inflammation and epithelial damage compared with wild-type controls, but the increase in microvascular permeability was similar in both types of mice *(82)*. These studies indicate clearly that exposure to ozone at low levels elicits activation of inflammatory cells, which release proinflammatory mediators that amplify inflammation.

Production of platelet-activating factor (PAF)

PAF is a potent bioactive phospholipid-derived mediator that causes bronchoconstriction and oedema, having a potency orders of magnitude higher than that of histamine. PAF also induces leukocyte chemotaxis, and can be elaborated by a variety of cell types (platelets, basophils, mast cells, neutrophils, macrophages and endothelium) either in cell-bound or secreted form. The participation of PAF in the pathogenesis of the acute effects of ozone has been supported by in vitro studies *(83)* as well as by in vivo studies in guinea-pigs *(59)* and mice *(84)*.

Increase in levels of nitric oxide

Nitric oxide is synthesized by the enzyme nitric oxide synthase (NOS), which occurs in the lungs in two forms – endothelial (eNOS) and inducible (iNOS) – and is produced by endothelial cells and macrophages. Both animal and human data provide support for the role of nitric oxide in mediating ozone-dependent injury. Mice deficient in iNOS (C57Bl/6Ai-[KO]NOS2 N5) exposed to 2 mg/m^3 ozone for six hours per night had significantly more severe inflammation (bronchial lavage protein content, MIP-2 and MMP-9 content and polymorphonuclear leukocytes) than wild-type controls. Pre-treatment of guinea-pigs with NOS inhibitors reduced airway hyperresponsiveness and neutrophil accumulation five hours after a single exposure to ozone and also reduced IL-8 mRNA expression in epithelial cells, indicating that endogenous nitric oxide plays an important role in persistent airway inflammation and hyperresponsiveness through upregulation of IL-8 *(85)*. Measurements of exhaled nitric oxide in children attending summer camp revealed that ambient ozone produces an acute inflammatory response in children even at levels slightly lower than currently prescribed by air quality guidelines *(86)*, but such findings are not corroborated by controlled human studies *(87)*.

Release of lysosomal enzymes

Activation of leukocytes and macrophages consequent to the release of inflammatory mediators after ozone exposure promotes the release of lysosomal proteases. In the extracellular space, these proteases may promote cell damage and digestion of the fibres of the collagenous and elastic systems, amplifying inflammation and airway and parenchymal remodelling. Airways and lung parenchyma contain anti-proteases that control the action of such enzymes in the extracellular environment. There is some evidence that ozone increases the release of proteases and may impair the efficiency of the anti-proteases.

Ozone exposure inhibits the activity of human alpha 1-proteinase inhibitor, alpha 1-antichymotrypsin, bronchial leukocyte proteinase inhibitor and Eglin C *(88)*. Inhalation of ambient levels of ozone did not cause significant alteration of anti-proteases in rats and humans *(89)*. On the other hand, in a study of 23 healthy non-smoking volunteers exposed to ambient levels of ozone, Nadziejko et al. *(90)* reported a significant increase in total neutrophil elastase-inhibitory capacity in BAL fluid. In asthmatics exposed to ozone, the treatment recombinant antileukoprotease, one of the major serine proteinase inhibitors in the lung, did not affect the immediate decrease in FEV_1 and increase in airway resistance after a single ozone exposure *(91)*. However, guinea-pigs treated with ONO-5046, a specific neutrophil elastase inhibitor, had a significant protective effect on late (five hours after exposure) neutrophil recruitment and airway hyperresponsiveness *(92)* and mucus discharge by goblet cells induced by a single ozone exposure (6 mg/m^3 for three hours) *(93)*.

Endothelial cell activation

Under the inputs provided by the series of inflammatory mediators listed above, pulmonary endothelium is activated and actively participates in the process of leukocyte adhesion and transmigration from the blood to pulmonary tissue. Leukocyte recruitment to inflammatory sites is dictated by complementary adhesion molecules expressed in leukocytes and endothelial membranes, which have their expression and affinity increased by inflammatory mediators. By and large, adhesion molecules belong to four families: selectins, immunoglobulin-like proteins, integrins and mucin-like glycoproteins. The intensity and timing of expression of these molecules provide important clues about the inflammatory process induced by exposure to ozone.

Healthy non-smokers exposed to ozone for two hours had an increased number of vessels exhibiting P-selectin 1½ hours later, despite the absence of changes in pulmonary function or cell counts in BAL samples *(63,94)*, indicating that upregulation of P-selectin could signify an early inflammatory response to ozone (such as margination and rolling of the neutrophils on the vessel wall) prior to transendothelial migration. In a study comparing healthy volunteers to asthmatics after exposure to 400 μg/m^3 for two hours, Stenfors et al. *(95)* reported a significant increase of neutrophils in BAL fluid, as well as increased expression of the endothelial adhesion molecules ICAM-1 and P-selectin 16 hours after exposure, without evidence of increased intensity of such events in asthmatics.

Activation of pulmonary endothelium mediates neutrophil recruitment. Cultured bovine pulmonary endothelial cells exposed to ozone at concentrations of up to 2 mg/m^3 exhibited a concentration-dependent decrease in prostacyclin, a potent vasodilator *(96)*. In the same study it was shown that pulmonary hypoxic vasoconstriction was augmented in dogs previously exposed to 2 mg/m^3 ozone. Healthy volunteers exposed for two hours to a combination of concentrated ambient particles (150 μg/m^3) and ozone (240 mg/m^3) showed significant brachial artery vasoconstriction *(97)*, indicating that short-term inhalation of fine particulate air pollution and ozone at concentrations that occur in the urban environment causes acute conduit artery vasoconstriction. Rats exposed for four hours to inhalation of 1.6 mg/m^3 ozone plus 49 mg/m^3 EHC-93 (Ottawa particles) showed higher mRNA levels of preproendothelin-1 and endothelin-converting enzyme after two hours of exposure; this is consistent with the notion of increased synthesis and conversion of the peptide endothelin-1 in lung endothelial cells, indicating that lung endothelin system genes respond rapidly and transiently to inhalation of urban pollutants *(98)*. Non-smoking healthy adults exposed to a combination of $PM_{2.5}$ (147 mg/m^3) and ozone (240 mg/m^3) exhibited an increase in diastolic blood pressure of 6 mmHg after two hours *(99)*. Such findings suggest that activation of pulmonary endothelium may take part in the pathogenesis of ozone-induced cardiovascular events reported by recent epidemiological studies.

Induction of systemic inflammatory reaction

Ozone inhalation does not induce an inflammatory process only in the lung. On the contrary, there are indicators that a systemic response may be triggered by ozone. Children living in areas with high ozone levels exhibited toxic granulations in circulating neutrophils and schistocytes, higher serum levels of IL-10 and IL-6 and lower levels of IL-8 than controls *(100)*. Exposure of rats and guinea-pigs to 200 mg/m^3 ozone for two weeks was shown to increase blood cholesterol levels *(101)*. Rats exposed to 200–400 mg/m^3 ozone for three hours exhibited increased production of nitric oxide by hepatocytes and enhanced protein synthesis, suggesting that ozone may trigger an acute phase response *(102)*. The real impact on health of this subclinical inflammatory reaction elicited by ozone exposure has yet to be determined.

Time course of inflammation induced by ozone

Adaptation to ozone is a well-known though still not fully understood event, being characterized by an attenuation of the decrement of pulmonary function that usually occurs after one or two consecutive exposures *(103–105)*. In terms of spirometric parameters, the duration of adaptation to ozone lasts for about one week, but may be longer if measurements of bronchial reactivity are considered *(106–108)*. To evaluate the real significance of the adaptation it is necessary to consider the mechanisms of ozone-dependent changes in pulmonary mechanics.

Ozone inhalation modifies pulmonary mechanics by reflex and inflammatory phenomena, which may not proceed at the same pace. Exposure to ozone increases the sensitivity of pulmonary C-fibres to several noxious stimuli, owing probably to the effects of cyclooxygenase metabolites resulting from epithelial injury *(109,110)*. Bronchopulmonary C-fibre stimulation reflexly reduces tidal volume and increases the respiration rate, constricts the airways, increases mucus secretion in the airways, and is associated with coughing. It has been consistently demonstrated that the inhalation of ozone by humans results in a reduction in transpulmonary pressure at maximal inspiratory volume without a concomitant decrease in lung compliance, demonstrating that the ozone-induced decrease in inspiratory capacity is not the result of an alteration in lung mechanics but of the stimulation of nerve endings located in the tracheobronchial tree and consequent inhibition of maximal inspiratory effort *(51)*. The stimulation of tracheobronchial C-fibres and rapidly adapting stretch receptors by ozone has been documented in animals *(111–113)*. Ozone-induced acute decrements of forced vital capacity (FVC) are most probably reflex in origin and not the result of breathing discomfort *(114,115)*. Thus, part of the acute effects of ozone on measurements of FEF or FVC is mediated by reflex phenomena. This implies a certain degree of dissociation between changes in pulmonary mechanics and inflammation as a consequence of inhalation of ozone. Significant correlations between inflammatory

cell counts in BAL and airway hyperresponsiveness were detected in guinea-pigs *(116)* and rats *(117)*, but human studies are not indicative of such a correlation. Healthy individuals classified as "least sensitive" and "most sensitive" on the basis of ozone-induced alterations in FEV_1, FVC and airway resistance showed increases of the same magnitude in cellular and biochemical markers of pulmonary inflammation in BAL (total and differential cell counts and total protein, fibronectin, IL-8 and granulocyte-macrophage colony-stimulating factor concentrations) 18 hours after exposure, pointing to a dissociation between injury/inflammation markers and the magnitude of decrements in pulmonary function *(118)*. No obvious association between decrements in pulmonary function and markers of inflammation measured in bronchial wash, BAL and bronchial biopsy was obtained in healthy volunteers inhaling 400 mg/m^3 ozone for two hours, indicating that the initial lung function decrements are not predictive of, or causally related to, the ozone-induced inflammatory events in normal subjects *(94)*. Indeed, despite the attenuation of pulmonary function alterations induced by repeated exposure to ozone, there is solid evidence that inflammation persists in the lower pulmonary parenchyma. Bonnet monkeys exposed to low levels of ozone for 90 days exhibited a concentration-dependent inflammation and structural remodelling at the level of the respiratory bronchioli *(15)*. In rats *(119,120)* and guinea-pigs *(121)*, structural damage and inflammation in the respiratory bronchioli were demonstrated in the course of acute functional adaptation to ozone. Healthy volunteers showed significant reductions in the number of polymorphonuclear cells, fibronectin and IL-6a after four days of exposure compared with exposure for only one day, indicating that the inflammation persists (though attenuated) in both proximal airways and distal lung with repeated daily exposures *(122)*. In a field study, in which repeated measurements of inflammatory markers in nasal lavage (eosinophil cationic protein, albumin and leukocytes) were performed in children exposed to ambient levels of ozone, Kopp et al. *(123)* identified acute inflammation of the nasal mucosa after the first increase in ambient ozone levels, a significant dose-dependent increase in leukocyte and eosinophil cationic protein levels, and some degree of adaptation during the summer season. Healthy volunteers exposed to 400 mg/m^3 ozone either for a single day or for four consecutive days exhibited adaptation after repeated exposures in terms of spirometry and differential cell counts in BAL, but the concentrations of total protein, IL-6, IL-8, reduced glutathione and orthotyrosine, and the numbers of neutrophils in bronchial mucosal biopsies were still elevated at the end of the four-day exposure protocol *(124)*. In fact, Frank et al. *(125)* proposed dividing the responses to repeated ozone exposure into two categories: adaptive and persistent, the persistence being preferentially located in the peripheral airways *(65,125)*.

Bronchopulmonary C-fibre stimulation also reflexly causes cardiovascular effects including bradycardia, a fall in cardiac output and bronchial vasodilation *(126)*. These effects may play a role in aggravating cardiovascular disease.

Mechanisms of ozone tolerance

The mechanisms responsible for adaptation to ozone are the result of upregulation of host defences. In vivo exposure to ozone has been demonstrated to reduce damage induced by exposure when tracheal explants of the same animals are exposed to ozone in vitro, indicating that the prevention of ozone damage by pre-exposures occurs in the absence of neural or systemic inputs *(127)*. Inhaled ozone reacts with several components of airway ELF, most of them acting as sacrificial reactants, thus minimizing oxidative damage to the underlying epithelium. With high ambient ozone levels, the balance between oxidation and antioxidative compounds is one of the determinants of the amount of damage produced. There is evidence that repeated exposure to ozone induces some degree of tolerance, owing presumably to upregulation of antioxidant defences such as increased mucin secretion *(128)*, uric acid *(129)*, ascorbic acid *(130)*, glutathione *(131)* and cytokines *(132)*.

Airway and pulmonary parenchyma remodelling

Ozone produces acute pulmonary inflammation at concentrations near those prescribed by air quality guidelines. Although the development of tolerance occurs after repeated or chronic exposure, it is now evident that inflammatory events persist even during the development of functional tolerance. The persistence of a subclinical inflammatory process may promote permanent damage to, or remodelling of, pulmonary structure. There is evidence that prolonged exposure to air pollutants induces inflammatory alterations, epithelial changes and functional impairment in rats chronically exposed to ambient air pollution *(133–135)*. Bronchiolar epithelial and smooth muscle hyperplasia and peribronchiolar fibrosis were detected in dogs living in areas with high levels of air pollution in Mexico City *(136)*. Centriacinar inflammatory changes *(137)*, bronchiolar fibrosis and epithelial hyperplasia *(138)* were detected in humans living in areas with high levels of air pollution. Since exposure to "real world" air pollution comprises simultaneous exposure to a range of toxic substances, considerable interest has been shown in the potential role of ozone in causing structural lung alterations in individuals living in areas with high levels of ambient air pollution.

Rats exposed for 90 days to 100 mg/m^3 ozone developed significantly remodelled distal airways, characterized by an increase in the volume of the terminal and respiratory bronchioli, the presence of fused basement membrane beneath reactive bronchiolar epithelium and alveolar ducts *(139,140)*. Some 7–10 weeks after rats were exposed for six hours daily to 160 mg/m^3 ozone and 14.4 ppm nitrogen dioxide they exhibited increased lung content of DNA, protein, collagen and elastin, and histopathological alterations that included severe fibrosis, alveolar collapse, honeycombing, macrophage and mast cell accumulation, vascular smooth muscle hypertrophy and other indications of severe progressive interstitial pulmonary fibrosis and end-stage lung disease *(141)*. Progressive remodelling

due to fibrosis in the centriacinar region of rats exposed simultaneously to ozone and nitrogen dioxide was associated with a sustained expression of mRNA for procollagen types I and III *(142)*. Exposure of rats to 100 mg/m^3 ozone for up to six months caused a significant mucous cell metaplasia of the nasal airway epithelium, which recovered after 13 weeks *(143)*. Exposure to ozone amplified mucus cell hyperplasia caused by ovalbumin inhalation in mice *(144)*.

A series of studies in primates also clearly demonstrated the potential of ozone to cause pulmonary remodelling. Bonnet monkeys exposed to 160 mg/m^3 ozone for 90 consecutive days (8 hours per day) developed increased quasistatic compliance of the lung and respiratory bronchiolitis, with hyperplasia of bronchiolar Clara cells *(145)*. Lung collagen content was markedly increased in rats and monkeys after prolonged (up to one year) exposure to ozone *(146)*. Long-term exposure of bonnet monkeys to ambient concentrations of ozone near 240 mg/m^3 induced significant nasal epithelial lesions (ciliated cell necrosis, shortened cilia, secretory cell hyperplasia and increased amount of stored mucosubstances), remodelling of distal airspaces (hyperplasia of nonciliated, cuboidal epithelial cells and intraluminal accumulation in respiratory bronchioles) *(9,10,16)*, fibrosis and smooth muscle hyperplasia of the respiratory bronchiolar wall *(15,147)* and muscular hypertrophy of pulmonary arterioles adjacent to respiratory bronchioli *(147)*. Rhesus monkeys exposed to ozone for six months exhibited a reduction in perlecan (a glycosaminoglycan of airway basement membrane) and abnormalities of the expression of fibroblast growth factor 2, fibroblast growth factor receptor 1 and syndecan-4, indicating that the structure and function of airway basement membranes are altered after chronic ozone exposure *(148,149)*. Infant atopic rhesus monkeys submitted to repeated cycles of acute injury and repair together with consecutive ozone and allergen exposures exhibited an increase in serum IgE, serum histamine and airways eosinophilia compared with allergen exposure alone. In addition, combined exposure to ozone and allergen resulted in greater alterations in airway structure, baseline airways resistance and reactivity *(150)*, as well as alterations in the normal structure and development of neural innervation at the level of the sixth and seventh intrapulmonary airway generations *(151)*. These results may provide the basis for chronic effects of ozone disclosed by epidemiological studies (see below).

Effects on immunity

Ozone may disrupt the function of the airway and pulmonary immune system, either by suppressing or by enhancing immune responsiveness *(152)* and reducing immune defences. Mice exposed to ozone have a lower resistance against inhaled *Staphylococcus aureus* in a dose-dependent manner *(153,154)*. Rats exposed to 600 μg/m^3 ozone in a regimen of four hours per day, five days per week for one or three weeks had a reduced clearance of *Listeria monocytogenes* challenge, with recovery after three weeks, with effects manifesting at the level of the

pulmonary alveolar macrophages and in the cytokine network responsible for immunoactivation *(155)*. In vitro exposure to ozone reduced the phagocytic capacity of alveolar macrophages *(156,157)* and their ability to respond to the activating cytokine interferon-gamma, reducing their reactive oxygen intermediate production and phagocytic activity *(158)*. Ozone exposure decreased the ability of surfactant protein A to modulate proinflammatory cytokine production by cells of monocyte/macrophage lineage, probably because of a decreased ability to activate the NFκB pathway, indicating that products generated by surfactant oxidation impair macrophage function and thus weaken local defences against inhaled pathogens *(159)*.

On the other hand, ozone may increase allergic response. Exposure increased bronchial responsiveness to allergen in people with airway allergy *(124)* as well as in animals *(160,161)*, including primates *(150)*. In mice, ozone induced a Th2-like immune response *(162)*, supporting the concept that it directs the immune response towards a Th2 pattern under certain conditions *(163)*. Ozone exposure does not increase allergic sensitization, but enhances antigen-induced airway inflammation in mice that are sensitized via the airways *(164)*. Moreover, ozone increases antigen-presenting activity and stimulates antigen-specific T-cell proliferation in rats, an event that may aggravate allergy symptoms *(165,166)*.

Factors defining susceptibility and tolerance to ozone

Functional and inflammatory responses to ozone show marked variation among individuals, indicating that susceptibility varies widely. The variable response is mainly dependent on age, previous health status and genetic make-up *(167,168)*.

Epidemiological evidence is consistent in identifying children and elderly people as preferential targets for some of the toxic effects of ozone *(169)*. Neonatal rats developed a more severe inflammation (prostaglandin E2, protein, lactate dehydrogenase and percentage of polymorphonuclear cells in BAL) than adult animals when exposed to ozone *(170)*. Old rats had a greater amount of epithelial injury in alveolar ducts and terminal bronchioles than adult rats when submitted to a single exposure of ozone at 160 mg/m^3 *(171)*. Old rats also showed an increased production of interleukin-6 after a single day or four consecutive days of exposure to ozone compared with juvenile and adult rats *(172)*. Immature and aged rats exhibited greater susceptibility to ozone (in terms of lung oxidative stress) than adult animals *(173)*. The increased damage induced by ozone is related to the reduced ventilatory response of this particular age group, which leads to an increased inhaled dose *(173,174)*. Arito et al. *(175)* reported that aged rats also have a slightly reduced ventilatory response to ozone in comparison to young adults.

However, evidence for greater effects of ozone in older individuals has not been found in controlled exposure experiments. Drechsler-Parks et al. *(176)*, comparing changes in pulmonary function in healthy humans aged 51–76 years,

suggested that older people may be less responsive to ozone than young people. In a study that analysed data collected on 290 male volunteers aged 18–32 years, exposed to one of six concentrations of ozone between 0.0 and 800 mg/m^3, a decreasing response was reported with increasing age for all ozone concentrations above zero *(177)*. Frampton et al. *(178–180)*, evaluating the response to a single exposure to ozone in healthy volunteers and smokers, found no effect of age on the magnitude of pulmonary mechanics response.

In line with recent epidemiological data that indicate an increased incidence of asthma in those who are overweight, obese mice exhibited a greater response to ozone *(181)*. This raises the possibility that serum leptin modulates the levels of the chemokine MIP-2 following acute ozone exposure and suggests that pro-inflammatory mediators may contribute to the development of airway inflammation in the obese. Epidemiological studies have shown asthmatics to be particularly sensitive to ozone, and thus several studies have looked for the biological plausibility of this association. Asthmatics exposed to 480 mg/m^3 ozone had a more intense inflammatory response detected in nasal lavage (cell counts and IL-8) than healthy controls *(182)*. Asthmatics had significantly greater increments in percentage of neutrophils and total protein concentration in BAL than non-asthmatics after a single exposure to ozone (400 mg/m^3 for four hours with moderate exercise), despite non-significant differences in pulmonary mechanics and lower respiratory symptoms *(183)*. In vitro exposure to ozone of airway epithelial cells from asthmatics caused a more intense secretion of cytokines than cells from healthy individuals *(76)*. After exposure to 400 mg/m^3 ozone for two hours, asthmatics had a greater expression of epithelial cytokines than healthy volunteers, showing a more intense increase in expression of IL-5, GM-CSF, ENA-78 and IL-8; the authors suggest that ozone-induced upregulation of Th2-related cytokines and neutrophil chemoattractants shown in the asthmatic group may contribute to a subsequent worsening of the airway inflammation *(184)*. Mild asthmatics were more responsive than healthy people to ozone in terms of exaggerated neutrophil recruitment or exacerbation of pre-existing allergic inflammation six hours after exposure to 400 mg/m^3 for two hours) *(95)*.

The effects of smoking on susceptibility to ozone are not so clear. Healthy volunteers and smokers with different grades of responsiveness to ozone did not differ in the inflammatory response elicited by a single exposure to 440 mg/m^3 ozone for four hours *(178–180,185)*.

Genetic components significantly influence the response to ozone. The magnitude of airway hyperresponsiveness differs among different rat strains. Lewis, BDII and Long-Evans rats developed airway hyperresponsiveness 90 minutes after exposure to ozone at ambient levels (100 mg/m^3), whereas other strains did not *(186)*. Susceptibility of mice to ozone has been shown to be influenced by their isoform of Clara-cell protein and permeability of the lung epithelial barrier *(187)*. There are candidate genes for ozone susceptibility, identified by linkage

analysis in mice: tumour necrosis factor-alpha in chromosome 17 *(188)*, Toll-like receptor in chromosome 4 *(189)* and small inducible cytokines in chromosome 11 *(190)*. In an association study in humans, the variability of response to ozone was associated with polymorphism of quinone metabolizing enzymes *(191)*.

Tables 1–3 depict the basic results of functional alterations, morbidity and mortality, respectively, resulting from exposure to ozone.

Table 1. Representative studies relating acute alterations in pulmonary function to markers of inflammation and ozone

Ozone concentration ($\mu g/m^3$)	Exposure duration	Sample	Procedure
800	2 h during exercise	Adults	Nasal lavage and BAL, cell counts and biochemistry
800	2 h	Adults	Oxidative stress (8-isoprostrane in exhaled breath)
800	2 h during mild exercise	Adults	Pulmonary function and eicosanoid levels in BAL fluid
800	2 h during exercise	Adults (healthy and asthmatic)	Spirometry and metabolites of cyclooxygenase in induced sputum
800	2 h during mild exercise	Adults	BAL, cell counts and biochemistry
700	75 min during intermittent exercise	Adults (females known to be responsive to ozone)	Pulmonary function
600	1 h	Adults	Pulmonary function, BAL and cell count
600	4 d, 5 h/d	Adults	Pulmonary function, acoustic rhinometry, nasal lavage, biochemistry
540	2 h	Adults with mild or persistent asthma	Sputum cell counts, inflammatory mediators and spirometry
540	2 h	Adults with mild atopic asthma who underwent allergen challenge 24 h before ozone exposure	Pulmonary function, cell counts in sputum
440	4 h during intermittent exercise	Adults (smokers and non-smokers)	BAL and nasal lavage (immediately and 18 h after exposure) for cell counts and interleukin determination
400	2 h during intermittent exercise	Adults	Pulmonary function, bronchial biopsy, bronchial wash function was assessed pre- and immediately post-exposure. Bronchoscopy was performed with endobronchial mucosal biopsies, bronchial wash, BAL and biochemistry.

Effect	Reference
Increased neutrophil counts were detected in nasal lavage immediately post-exposure, lasting for 18 h. Neutrophils and albumin increased in BAL 18 h after exposure.	Graham et al. *(192)*
Increase oxidative stress 4 h after exposure.	Montuschi et al. *(69)*
Increased respiratory symptoms, bronchoalveolar cell counts, specific airway resistance. No change in cyclooxygenase metabolites.	Coffey et al. *(72)*
Similar reductions in FVC (asthmatics = 12%, healthy = 10%). Small airway function showed the greatest ozone-induced decline in asthmatics. Post-exposure levels of PGF2-α were significantly elevated in asthmatics compared to healthy volunteers.	Alexis et al. *(73)*
Decrements of pulmonary function, increase in inflammatory cells and IL-6. Antioxidants in the diet attenuated changes in pulmonary function but not inflammatory cell or interleukin increases.	Samet et al. *(193)*
Airway obstruction and bronchial hyperresponsiveness immediately after exposure, these changes decreasing after 18 h and returning to baseline levels after 42 h.	Folinsbee et al. *(194)*
FEV_1 was significantly reduced 1 h after exposure, returning to pre-exposure values at 6 h and 24 h after, but neutrophils in BAL elevated at 6 h and 24 h after exposure.	Schelegle et al. *(195)*
No changes in cell counts of levels of IL-1 or IL-8 or dimensions of nasal cavity. Decreases in PEF, FEV_1, and FVC, as well diminished effect of deep inspiration on forced expiratory flows.	Kjaergaard et al. *(196)*
Increases in neutrophil counts and IL-8 in sputum and decreases in FEV_1. Cell recruitment and interleukin increase (but not pulmonary function alterations) were prevented by previous treatment with corticosteroids.	Vagaggini et al. *(197)*
Greater severity of asthma late phase response after ozone exposure, characterized by higher counts of eosinophil and increase in bronchial obstruction.	Vagaggini et al. *(198)*
Leukocytes (PMN) increased by up to 6-fold late after ozone exposure. IL-6 and IL-8 increased early (by up to 10-fold and up to 2-fold, respectively) and correlated with the late increase in PMN. Lymphocytes, mast cells and eosinophils also increased late after exposure.	Torres et al. *(185)*
Adhesion molecule upregulation, increased submucosal mast cell numbers, alterations to the respiratory tract lining fluid redox status, and obstructive changes in pulmonary function. No clear relationship between changes in inflammatory markers and lung function.	Blomberg et al. *(94)*

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Ozone concentration (µg/m³)	Exposure duration	Sample	Procedure
400	2 h during intermittent exercise	Adults	BAL, cell counting, biochemistry, lymphocyte subtyping, immunohistochemistry
400	2 h	Adults with mild asthma	Bronchial biopsy, immunohistochemistry
400	2 h	Adults with mild asthma and controls	Bronchial biopsy, bronchial lavage, immunohistochemistry
400	4 h during mild exercise (single or repeated 4-h exposures over 4 days)	Adults	Pulmonary function, bronchial biopsy, BAL, biochemistry
400	2 h during intermittent exercise	Adults	Nasal lavage and blood sampling, bronchial biopsy, cell counts and biochemistry
400	2 h during intermittent exercise	Adults	Pulmonary function, bronchial biopsy, BAL, biochemistry
400	4 h during mild exercise (single or repeated 4-h exposures over 4 days) during mild exercise	Adults	Pulmonary function, BAL and biochemistry
400	4 h during intermittent exercise	Adults (controls, asthmatics, smokers)	Pulmonary function, bronchial hyperresponsiveness, BAL and biochemistry up to 18 h after exposure
400	4 h during intermittent exercise	Adults (controls and asthmatics)	Symptoms, pulmonary function, BAL, cell count, biochemistry
400	2 h	Adults	Pulmonary function and plasma levels of Clara cell protein (before, immediately after, 2 h and 4 h post-exposure)

Effect	Reference
Increase in the proportion of PMNs, IL-8, Gro-alpha and total protein ($P = 0.058$) in BAL fluid 6 h after exposure. Decrease in the CD4 : CD8 ratio and the proportion of activated CD4+ and CD8+ T cells. No significant changes demonstrable in any of the inflammatory markers studied in the biopsies.	Krishna et al. *(199)*
Increases in epithelial expression of IL-5, GM-CSF, ENA-78 and IL-8 6 hours after exposure.	Bosson et al. *(184)*
Ozone induced similar increases in bronchial wash neutrophils in both groups increased expression of P-selectin and ICAM-1, as well as increasing tissue PMN and mast cell numbers in healthy volunteers.	Stenfors et al. *(95)*
Single exposures induced significant decrements of pulmonary function and markers of inflammation. Repeated exposure led to no effect lung function and differential cell counts in BAL, but the concentrations of inflammatory markers were still increased.	Jorres et al. *(124)*
Reduction in nasal ascorbic acid, reduced glutathione, extracellular superoxide dismutase and myeloperoxidase. Uric acid, total protein and albumin concentrations did not display washout kinetics.	Mudway et al. *(200)*
Upregulation in the expression of vascular endothelial P-selectin and ICAM-1, as well as an increase in submucosal mast cells in biopsy samples and increase of reduced glutathione. Obstructive alterations in pulmonary function were observed immediately after exposure.	Blomberg et al. *(94)*
At 20 h after exposure, increases in inflammatory markers in BAL (total protein, LDH, fibronectin, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and number of PMN), as well as in pulmonary conductance, inflammatory and pulmonary function alterations were attenuated after 4-day exposure.	Christian et al. *(122)*
In normal subjects, ozone induced increases in percentage of PMN, total protein concentration, increased percentage of PMN and increased expression of ICAM-1 in bronchial mucosa. Asthmatics tended to have greater inflammatory response. Smokers experienced smaller decrements in lung function and fewer symptoms than nonsmokers, but the intensity of the airway inflammatory response was independent of smoking status. Cytokine expression increased acutely and may persist for weeks after exposure.	Frampton et al. *(178–180)*; Balmes et al. *(183)*
18 h after exposure, asthmatics exhibited significantly more severe effects on FEV_1, FVC, specific airway resistance, lower respiratory symptoms, percentage of PMNs, total protein and IL-8 in the bronchial fraction, and percentage of PMNs, total protein, LDH, fibronectin, IL-8, GM-CSF, and MPO in BAL.	Scannell et al. *(201)*
Increased Clara cell protein serum concentrations at 2 h and 4 h post-exposure. No association between increased Clara cell protein concentrations and lung function changes.	Blomberg et al. *(202)*

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Ozone concentration (µg/m³)	Exposure duration	Sample	Procedure
240 and 800	2 h during intermittent exercise	Adults	Cell counts in nasal lavage and induced sputum. Plasma concentration of 2, 3-dihydroxybenzoic acid (2,3-DHBA, a salicylate metabolite and an indicator for hydroxyl radical)
240	2 h	Adults	Pulmonary function, bronchoscopy, bronchial biopsy, BAL, biochemistry, immunoperoxidase
240–800	2 h	Adults	Pulmonary function
240–480	90 min during intermittent exercise	Adults (healthy and asthmatic)	Pulmonary function tests, posterior rhinomanometry and nasal lavage (inflammatory mediators and biochemistry
240–480	1 h during heavy exercise	Endurance athletes	Endurance symptoms, pulmonary function
240–800	2½ h during intermittent exercise for 2 h	Adults	Pulmonary function
240 and 400	60 min during maximal exercise	Adults (endurance cyclists)	Pulmonary function
240	6.6 h during intermittent exercise over 5 consecutive days	Adults	Pulmonary function
240	2.3 h during intermittent exercise	Adults	Pulmonary function
200	2 h during intermittent exercise	Adults	Markers of oxidative stress (exhaled breath and plasma)
160–240	6.6 h during intermittent exercise	Adults	Pulmonary function
160 and 200	2 h during exercise	Adults	BAL (18 h after exposure) for determinations of inflammatory markers
64–206	2 h to ambient levels during bicycle rides	Adults	Plasma levels of Clara cell protein (CC10 or CC16)

Effect	Reference
Increased PMN counts in sputum at the higher dose. No alterations in nasal lavage. Plasma 2,3-DHBA concentration increased significantly following exposure to 240 µg/m^3 ozone.	Liu et al. *(203)*
1 h after exposure, no changes in FEV_1, FVC or any inflammatory indices in the bronchial wash and BAL fluid. No significant differences were seen in inflammatory cell numbers or percentages of vessels expressing VCAM-1, E-selectin or ICAM-1 in the biopsies, but the percentage of vessels expressing P-selectin increased significantly after exposure.	Krishna et al. *(61–63)*
Acute decrements of pulmonary function. Effects decreased with age, were modified by social economic status and had no influence on menstrual cycle.	Seal et al. *(204)*
In subjects with asthma, a significant increase in white blood cells in BAL was detected both immediately and 24 h after exposure to 480 µg/m^3 ozone, as was a significant increase in epithelial cells immediately after exposure. No significant cellular changes were seen in non-asthmatics. A significant correlation was observed between IL-8 and WBC counts after exposure to ozone (r = 0.76) in asthmatics. No significant changes in pulmonary or nasal function or biochemical mediators were found in either asthmatics or non-asthmatics.	Mcbride et al. *(182)*
Increase in epithelial cells immediately after exposure. No significant cellular changes were seen in non-asthmatics. A significant correlation was observed between IL-8 and WBC counts after exposure to ozone (r = 0.76) in asthmatic subjects. No significant changes in pulmonary or nasal function or biochemical mediators were found in either asthmatics or non-asthmatics.	Schelegle et al. *(205)*
Changes in FVC, FEV_1 and mean expiratory flow rate between 25% and 75% FVC were observed at 240 and 360 µg/m^3.	Mcdonnell et al. *(167)*
Decrease in FEV immediately after exercise, more intense the higher the dose. Aerobic performance was impaired at the higher dose.	Gong et al. *(206)*
Pulmonary obstruction observed during the first 2 days and adaptation occurring for the last 3 days.	Folinsbee et al. *(207)*
Increase in airway resistance and decrease in spirometric parameters for all concentrations.	Seal et al. *(208)*
Evidence of oxidative stress in exhaled breath but not in plasma. Response was affected by polymorphism of genes encoding for antioxidant enzymes.	Corradi et al. *(209)*
Indications of pulmonary obstruction and increased airway hyperresponsiveness for all ozone concentrations.	Horstman et al. *(210)*
Increases in neutrophils, PGE_2, fibronectin, IL-6 and LDH.	Devlin et al. *(211)*
Positive association between ambient ozone levels and increase of plasma levels of Clara cell proteins, suggesting that low levels of ozone increase airway epithelial permeability.	Broeckaert et al. *(212)*

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Ozone concentration (µg/m³)	Exposure duration	Sample	Procedure
64–206	2 h to ambient levels during bicycle rides	Adults	Pulmonary function, PCR (NAD(P)H: quinone oxidoreductase and glutathione-S-transferase micro-1 polymorphism, plasmatic levels Clara cell protein CC16, and measurements of 8-hydroxy-2′-deoxyguanosine (adduct in DNA of peripheral leukocytes)
44–148	Ambient exposure during hiking	Adults (controls, asthmatics, history of wheeze and former smokers)	Pulmonary function
40–220	Ambient levels in 3 communities in Taiwan, China	Primary school children	Pulmonary function
40–157	Ambient levels in two communities in Switzerland	Children during 10-min exercise	Pulmonary function
40–490	Ambient levels of a summer camp in California	Children and young adults (9–35 years of age)	Pulmonary function
30–250	Ambient levels in the Netherlands	Cyclists during regular training (15–135 min)	Pulmonary function
22–380	Ambient levels of Leyden	Adults with intermittent or severe asthma	Pulmonary function and broncho-provocation
10–179	Ambient levels in 2 communities in Germany	Schoolchildren	Pulmonary function
11–249	Ambient levels of a community in Taiwan, China	Adults (mail carriers)	Peak expiratory flow (morning and night)

Effect	Reference
Exposures to >160 μg/m^3 resulted in significant decrements of pulmonary function tests and increased levels of serum CC16. (NAD(P)H:quinone oxidoreductase and glutathione-S-transferase micro-1null subjects showed functional changes, increased serum CC16 and DNA adducts.	Bergamaschi et al. *(191)*
A 2.6% decline in FEV_1 and a 2.2% decline in FVC for each 100 μg/m^3 increment in mean ozone after adjustment for age, sex, smoking status (former vs never), history of asthma or wheeze, hours hiked, ambient temperature and other covariates. Hikers with asthma or a history of wheeze had 4-fold greater responsiveness to ozone than others.	Korrick et al. *(213)*
Significantly negative association of peak ozone on the day before spirometry with individual FVC and FEV_1. Alterations occurred at peak hourly ozone concentrations <160 μg/m^3.	Chen et al. *(214)*
Negative association between ozone levels measured during exercise and PEF. The slope average adjusted regression coefficient for delta-PEF on ozone was –2.28 ml/s/μg/m^3 (95% CI).	Braun-Fahrlander et al. *(215)*
Ambient levels of ozone related negatively with pulmonary function. Average regression coefficient for FEV_1 on ozone was –0.39 ml/ppb, –0.78 ml per μg/m^3, and for FVC –0.88 ml per μg/m^3.	Higgins et al. *(216)*
The slopes of the regression models relating ozone to FVC, FEV_1 and PEF were –0.39, –0.35 and –1.54 ml per μg/m^3 ozone, respectively. Supplementation with antioxidants reduced the detrimental effects of ozone.	Grievink et al. *(217)*
Positive associations between ozone and respiratory symptoms and bronchodilator use. An increase of 100 μg/m^3 was associated with decreases of –1.0, –08, –3.2 and –0.7 l/min of peak expiratory flow at lags 0, –1, –2 and –3, respectively. Effects of ozone were more intense than those observed for PM_{10}, nitrogen dioxide and black smoke. Response to ozone was not influenced by severity of asthma.	Hiltermann et al. *(218)*
Negative associations between vital capacity and ozone levels the previous day.	Ulmer et al. *(219)*
Night PEFR and the deviation in night PEFR were significantly reduced in association with 8-h ozone exposures with a lag of 0–2 days and by daily maximum ozone exposures with a lag of 0–1 days. No effects of PM_{10} or nitrogen dioxide. For a 20 μg/m^3 increase in the 8-h average ozone concentration, the night PEFR was decreased by 0.54% for a 0-day lag, 0.69% for a 1-day lag and 0.52% for a 2-day lag.	Chan et al. *(220)*

Table 2. Representative studies relating hospital admissions to ambient ozone concentrations

Location	End-point	Other pollutants considered
New Jersey	Hospital admissions for asthma	
Birmingham, Alabama	Hospital admissions for respiratory diseases in the elderly	PM_{10}
Ontario	Hospital admissions for respiratory diseases	Sulfates
Minneapolis–St Paul	Hospital admissions for respiratory diseases in the elderly	PM_{10}
Detroit	Hospital admissions for respiratory diseases in the elderly	PM_{10}
Montreal	Emergency respiratory admissions	PM_{10} and sulfates
Detroit	Hospital admissions for cardiovascular diseases	PM_{10}, carbon monoxide and sulfur dioxide
Barcelona	Emergency department visits for asthma	Black smoke, sulfur dioxide and nitrogen dioxide
Chicago, Detroit, Houston, Los Angeles, Milwaukee, New York and Philadelphia	Hospital admissions for congestive heart failure	Carbon monoxide, nitrogen dioxide, sulfur dioxide and ozone
Spokane	Hospital admissions for respiratory diseases	PM_{10}
Rotterdam and Amsterdam	Emergency hospital visits for respiratory diseases	Sulfur dioxide, nitrogen dioxide and black smoke
Paris	Hospital admissions for respiratory diseases	PM_{13}, black smoke, sulfur dioxide and nitrogen dioxide

Observed effect	Reference
Positive and dose-dependent association between ozone and hospital admissions for asthma.	Cody et al. *(221)*
Positive and dose-dependent association between ozone and PM_{10} and hospital admissions for respiratory diseases in elderly people. An increase of 100 μg/m^3 ozone was associated with admissions for pneumonia with a 2-day lag (RR = 1.14, 95% CI 0.94–1.38) and for COPD with a 1-day lag (RR = 1.17, 95% CI 0.86–1.60).	Schwartz *(222–224)*
5% of daily respiratory admissions in May–August were associated with ozone, with sulfates accounting for an additional 1%. Ozone was a stronger predictor of admissions than sulfates. Positive and statistically significant associations were observed between the ozone–sulfate pollution mix and admissions for asthma, COPD and infections. Positive associations were also found in all age groups, with the largest impact on infants (15% of admissions associated with the ozone–sulfate pollution mix) and the smallest effects on the elderly (4%).	Burnett et al. *(225)*
An increase in daily ozone concentration of 100 μg/m^3 was associated with pneumonia admissions (RR = 1.15, 95% CI = 1.36–0.97). Significant effects of PM_{10} were also present.	Schwartz *(222)*
An increase in daily ozone concentration of 10 μg/m^3 was associated with hospital admissions for pneumonia in the elderly (RR = 1.026, 95% CI = 1.040–1.013) and COPD other than asthma (RR = 1.028, 95% CI = 1.049–1.007). Positive results for PM_{10}.	Schwartz *(223)*
No effect of ozone. Positive effects of PM_{10} and sulfates.	Delfino et al. *(226)*
No effect of ozone on cardiovascular admissions. Positive effects of PM_{10} and carbon monoxide.	Schwartz et al. *(227)*
No effect of ozone on respiratory admissions. Positive effects of black smoke and nitrogen dioxide.	Castellsague et al. *(228)*
No effect of ozone on hospital admissions for congestive heart failure. Positive effect of carbon monoxide.	Morris et al. *(229)*
Positive association (RR = 1.244, 95% CI = 1.002–1.544) for a 50-μg/m^3 increase in peak-hour ozone and hospital admissions for respiratory diseases. Positive effect of PM_{10}.	Schwartz *(230)*
Significant positive association with admissions for respiratory diseases (RR = 1.344 in Rotterdam but not in Amsterdam (risk for an increase of 100 μg/m^3)). No effects for the other pollutants considered.	Schouten et al. *(231)*
No effect of ozone on hospital admissions for respiratory diseases. Significant effects of PM_{13}, black smoke and sulfur dioxide	Dab et al. *(232)*

▶

Location	End-point	Other pollutants considered
London	Hospital admissions for respiratory diseases	Black smoke, sulfur dioxide and nitrogen dioxide
Helsinki	Hospital admissions for cardiac and cerebrovascular diseases	Sulfur dioxide, nitrogen dioxide and PM_{10}
Sixteen Canadian cities	Hospital admissions for respiratory diseases	PM_{10}, sulfur dioxide, nitrogen dioxide and carbon monoxide
Amsterdam, Barcelona, London, Milan, Paris and Rotterdam	Hospital admissions for COPD	TSP, black smoke, sulfur dioxide and nitrogen dioxide
Minneapolis–St. Paul	Hospital admissions for COPD and pneumonia among the elderly	PM_{10}, carbon monoxide, nitrogen dioxide and sulfur dioxide
Tucson	Hospital admissions for cardiovascular diseases	PM_{10}, carbon monoxide, nitrogen dioxide and sulfur dioxide
London, Amsterdam, Rotterdam, Paris and Milan	Hospital admissions for all respiratory causes	Black smoke and nitrogen dioxide
London	Hospital admissions for asthma	Black smoke, nitrogen dioxide and sulfur dioxide
Santiago de Chile	Visits to primary health care for respiratory diseases in children	PM_{10}
Toronto	Hospital admissions for respiratory, cardiac, cerebrovascular and peripheral vascular diseases	$PM_{2.5}$, PM_{10}, carbon monoxide, nitrogen dioxide and sulfur dioxide
São Paulo	Respiratory emergency visits in children	PM_{10}, carbon monoxide, nitrogen dioxide and sulfur dioxide
Hong Kong	Emergency visits for cardiovascular diseases	PM_{10}, sulfur dioxide and nitrogen dioxide
London	Emergency hospital admissions for respiratory and cardiovascular diseases	PM_{10}, black smoke, carbon monoxide, sulfur dioxide and nitrogen dioxide
Paris	Hospital admissions for asthma in children	Black smoke, sulfur dioxide and nitrogen dioxide

Observed effect	Reference
Ozone (lagged 1 day) was significantly associated with an increase in daily admissions among all age groups except the 0–14-year group, and this effect was stronger in the "warm" season (April–September). In this season, the RR of admission associated with an increase in 8-h ozone levels of 58 μg/m^3 (10th to 90th percentiles) were 1.0483 (95% CI 1.0246– 1.0726), 1.0294 (0.9930–1.0672), 1.0751 (1.0354–1.1163) and 1.0616 (1.0243–1.1003) for all ages and age groups 0–14, 15–64 and 65+, respectively. No effect of the remaining pollutants.	Ponce de Leon et al. *(233)*
Admissions for ischemic heart disease were significantly associated with the prevailing levels of ozone, and those due to cerebrovascular diseases were associated with nitrogen dioxide levels.	Ponka & Virtanen *(234)*
RR for an increase of 60 μg/m^3 ozone varied from 1.043 to 1.024 depending on model specifications. Positive effects for PM_{10} and carbon monoxide.	Burnett et al. *(235)*
RR for and increase of 50 μg/m^3 ozone (8-h mean) was 1.04 (1.02–1.07). Significant effects were detected for the remaining pollutants.	Anderson et al. *(236)*
An increase of 30 μg/m^3 was associated with a 5.15% increase in admissions. PM_{10}, sulfur dioxide and nitrogen dioxide also exhibited positive and significant associations.	Moolgavkar et al. *(237)*
No effect of ozone. Positive and significant associations for PM_{10} and carbon monoxide.	Schwartz *(238)*
Significant increase in daily admissions for respiratory diseases (adults and elderly) with elevated levels of ozone. This finding was stronger in the elderly, had a rather immediate effect (same or next day) and was consistent from city to city. No consistent effect of black smoke or nitrogen dioxide.	Spix et al. *(239)*
Ozone was significantly associated with admissions in the 15–64-year age group (10 ppb, 8-h average, 3.93% increase). All other measured pollutants showed positive and significant associations.	Anderson et al. *(240)*
For children 3–15 years of age there was an increase of 5% in lower respiratory symptoms for a 50-μg/m^3 increase in ozone level.	Ostro et al. *(241)*
Ozone was associated with admissions for asthma, COPD and respiratory infection, but no effect was detected for cardiovascular diseases. Significant effects were observed for the remaining pollutants.	Burnett et al. *(242)*
Significant effects of ozone (mostly for upper respiratory diseases) and PM_{10} (lower respiratory diseases).	Lin et al. *(243)*
Significant effect of ozone. RR = 1.03 for all seasons and all diseases for an increment of 50 μg/m^3. In cold season RR increased to 1.08. RR was higher for heart failure.	Wong et al. *(244)*
No effect of ozone. Significant effects for PM_{10} and sulfur dioxide.	Atkinson et al. *(245)*
An increase of 100 μg/m^3 ozone was associated with a RR of 1.52 (CI 1.06–2.19) for paediatric asthma admissions. No significant effects were observed for the remaining pollutants.	Fauroux et al. *(246)*

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Location	End-point	Other pollutants considered
London	Hospital admissions for wheezing episodes in children	Hydrocarbon species, nitrogen dioxide, sulfur dioxide and PM_{10}
Atlanta	Emergency department visits for asthma in children	PM_{10}
Los Angeles	Hospital admissions for cardiopulmonary illnesses	PM_{10}, carbon monoxide and nitrogen dioxide
São Paulo	Hospital admissions for pneumonia	PM_{10}, nitrogen dioxide, sulfur dioxide and carbon monoxide
Valencia	Emergency hospital admissions for cardiovascular diseases	Black smoke, carbon monoxide, nitrogen dioxide and sulfur dioxide
Toronto	Hospital admissions for acute respiratory problems in children <2 years of age	PM_{10}, sulfur dioxide, nitrogen dioxide and carbon monoxide
Belfast	Hospital admissions for acute asthma	PM_{10}, sulfur dioxide, nitrogen dioxide, carbon monoxide and benzene
Rome	Emergency hospital admissions for respiratory conditions	PM_{10}, nitrogen dioxide, sulfur dioxide and carbon monoxide
London	Consultations for respiratory diseases at family practices	PM_{10}, sulfur dioxide and nitrogen dioxide
Valencia	Emergency department visits for COPD	Black smoke, carbon monoxide, sulfur dioxide and nitrogen dioxide
São Paulo	Emergency department visits for chronic lower respiratory disease in people >64 years of age	PM_{10}, sulfur dioxide, nitrogen dioxide and carbon monoxide
South Coast Air Basin of California	Hospital admissions for ischemic heart disease	PM_{10}, nitrogen dioxide and carbon monoxide
Cincinnati	Emergency department visits and hospital admissions for asthma	PM_{10}
Cook County, Los Angeles County and Maricopa County	Hospital admissions for COPD	PM_{10}, carbon monoxide, sulfur dioxide and nitrogen dioxide
Madrid	Emergency department visits for asthma	Sulfur dioxide, nitrogen dioxide and PM_{10}

Observed effect	Reference
Incidence of wheeze relative to that at the mean ozone concentration of 32.7 μg/m^3 was estimated to increase by 65% (95% confidence interval = 22–122) at an ozone concentration of 5 μg/m^3 (1.5 standard deviations below the mean) and by 63% (95% CI 6–184) at 80 μg/m^3 (2.5 standard deviations above the mean). Positive associations were found for several hydrocarbons. No effects of nitrogen dioxide, sulfur dioxide and PM_{10} were observed.	Buchdahl et al. *(247)*
A 10-μg/m^3 increase in 8-h ozone level was associated with a RR of 1.04 in asthma admissions. Significant positive effects were also observed for PM_{10}. In two-pollutant models, ozone and PM_{10} became non-significant because of co-linearity.	Tolbert et al. *(248)*
No effect of ozone. Significant effects for the remaining pollutants.	Linn et al. *(249)*
No effect of ozone. Significant effect of PM_{10}	Braga et al. *(250)*
No effect of ozone. Significant effects of carbon monoxide and nitrogen dioxide.	Ballester et al. *(251)*
A 35% increase (95% CI 19–52) in the daily hospitalization rate for respiratory problems was associated with a 5-day moving average of the daily 1-hour maximum ozone of 90 μg/m^3 for the period May–August.	Burnett et al. *(252)*
No effect of ozone. Positive associations with remaining pollutants.	Thompson et al. *(253)*
Ozone was associated with admissions only among children (lag 1, 5.5% increase per interquartile range, 23.9 μg/m^3. Significant effects were observed for other gaseous pollutants.	Fusco et al. *(254)*
No effect of ozone. Positive associations with PM_{10} and sulfur dioxide.	Hajat et al. *(255)*
An increase of 10 μg/m^3 in ozone was associated with an excess of 3.9% (CI = 1.4– 6.6) in expected COPD. A positive and significant effect was observed for carbon monoxide. There was no significant association for the remaining pollutants.	Tenias et al. *(256)*
Interquartile range increases in the 4-day moving average of ozone (35.87 μg/m^3) increased emergency visits by 14%. Positive effects of sulfur dioxide.	Martins et al. *(257)*
No effect of ozone. Significant associations with carbon monoxide and nitrogen dioxide.	Mann et al. *(258)*
No effect of ozone. Significant association with PM_{10}.	Lierl et al. *(259)*
Ozone was associated with admissions during the period April–September but not with full-year analysis.	Moolgavkar *(260)*
A 10 μg/m^3 rise in ozone was associated with a RR of 1.045 (1.018–1.073) in asthma admissions. Positive associations also were observed for the remaining pollutants. The effect of ozone was not significantly affected by the inclusion of other pollutants or pollen counts.	Galán et al. *(261)*

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Location	End-point	Other pollutants considered
Denver	Hospital admissions for cardiovascular diseases in the elderly	PM_{10}, carbon monoxide, sulfur dioxide and nitrogen dioxide
Marseille	Emergency admissions for asthma	Sulfur dioxide and nitrogen dioxide
Kaohsiung	Hospital admissions for cardiovascular diseases	PM_{10}, nitrogen dioxide and carbon monoxide
Seoul	Hospital admissions for ischaemic cardiovascular diseases in the elderly	PM_{10}, carbon monoxide, sulfur dioxide and nitrogen dioxide
Taipei	Hospital admissions for cardiovascular diseases	PM_{10}, nitrogen dioxide and carbon monoxide
São Paulo	Emergency department visits and hospital admissions for respiratory diseases in children	PM_{10}, carbon monoxide, sulfur dioxide and nitrogen dioxide
Vancouver	Hospital admissions for respiratory diseases in children (<3 years) and the elderly	Carbon monoxide, nitrogen dioxide, sulfur dioxide and coefficient of haze
Portland and Manchester, USA	Emergency department visits for respiratory diseases	$PM_{2.5}$ and sulfur dioxide
Four Australian cities	Hospital admissions for respiratory diseases	Black carbon and nitrogen dioxide
South-west France	Hospital admissions for acute myocardial infarction, sudden death and probable cardiac death	Sulfur dioxide and nitrogen dioxide
Thirty-six cities in the USA	Hospital admissions for pneumonia and COPD	PM_{10} and ozone

Observed effect	Reference
Ozone was associated with an increase in the risk of hospitalization for acute myocardial infarction, coronary atherosclerosis and pulmonary disease. Significant associations were also observed for sulfur dioxide and carbon monoxide.	Koken et al. *(262)*
An increase of 10 μg/m^3 ozone was associated with a 6–10% increase in the risk of emergency admissions.	Boutin-Forzano et al. *(263)*
No effect of ozone. Positive association with carbon monoxide.	Yang et al. *(264)*
An increase of 44 μg/m^3 ozone exhibited a RR of 1.10 (95% CI 1.05–1.15). Significant associations were detected for the remaining pollutants.	Lee et al. *(265)*
No effect of ozone. Positive association with PM_{10}.	Chang et al. *(266)*
No robust effect of ozone. Positive associations with PM_{10} and carbon monoxide.	Farhat et al. *(267)*
Significant ozone associations where 24-h ozone maximum was 27 μg/m^3.	Yang et al. *(268)*
An increase of 10 μg/m^3 ozone was associated with a RR of 1.02 (95% CI 1–1.03) increase in emergency visits in Portland for asthma. Positive effects of sulfur dioxide were also detected No significant associations were found in Manchester, possibly due to statistical limitations of analysing a smaller population.	Wilson et al. *(269)*
RR of 1.007 per 10 μg/m^3 increase in ozone for asthma and COPD hospital admissions in the elderly.	Simpson et al. *(270)*
An increment of 5 μg/m^3 was associated with a RR of 1.05 for myocardial infarction. No effects of nitrogen dioxide and sulfur dioxide.	Ruidavets et al. *(271)*
An increase of 10 μg/m^3 ozone was associated with a 0.27% (CI 0.08–0.47) increase in COPD admissions and a 0.41% (CI 0.26–0.57) increase in pneumonia admissions. Significant associations also for PM_{10}.	Medina-Ramon et al. *(272)*

Table 3. Selected studies relating ambient variations of ozone concentrations to short-term mortality

Location	End-point	Other pollutants considered
São Paulo	Respiratory mortality in children	PM_{10}, nitrogen dioxide, sulfur dioxide and carbon monoxide
Philadelphia	All causes (excluding accidents)	TSP and sulfur dioxide
London	Total mortality, mortality in people >70 years, and cardiovascular and respiratory mortality	Black smoke, sulfur dioxide and nitrogen dioxide
Lyon	Total (minus external causes), respiratory, cardiovascular and digestive causes (as a control)	PM_{13}, sulfur dioxide and nitrogen dioxide
Barcelona	Total mortality, mortality in people >70 years, and cardiovascular and respiratory mortality	Black smoke, sulfur dioxide and nitrogen dioxide
Mexico City	All causes (excluding accidents)	TSP and sulfur dioxide
Philadelphia	All causes (excluding accidents), respiratory disease and cardiovascular disease	TSP, sulfur dioxide, nitrogen dioxide and carbon monoxide
Six cities in Europe	All causes (excluding accidents)	Black smoke, sulfur dioxide and nitrogen dioxide
Brisbane	Total, respiratory and cardiovascular	PM_{10}, nitrogen dioxide, sulfur dioxide, carbon monoxide and black smoke
Rotterdam	All causes (excluding accidents)	Black smoke, sulfur dioxide and carbon monoxide
Sidney	Total, respiratory and cardiovascular	Fine particles and nitrogen dioxide
Helsinki	Total and cardiovascular	TSP, sulfur dioxide and nitrogen dioxide
Eleven cities in Europe	Respiratory, cardiovascular and digestive (used as control)	Sulfur dioxide, nitrogen dioxide and different indicators of PM
Seoul and Ulsan	All causes (excluding accidents)	TSP and sulfur dioxide
Mexico City	All causes (excluding accidents) in children	$PM_{2.5}$, sulfur dioxide and nitrogen dioxide
Seoul	Deaths in patients with congestive heart failure	PM_{10}, nitrogen dioxide, sulfur dioxide and carbon monoxide

Observed effect	Reference
No effect of ozone. Positive association with nitrogen dioxide.	Saldiva et al. *(273)*
Ozone was associated with mortality in summer (RR = 1.15, 95% CI 1.07–1.24 for an increase of 200 μg/m^3). Positive effect of sulfur dioxide.	Moolgavkar et al. *(274)*
An increase of 8-h ozone from the 10th to the 90th percentile of the seasonal change (14–72 μg/m^3) was associated with increases of 3.5%, 3.6% and 5.4% in all cause, cardiovascular and respiratory mortality, respectively.	Anderson et al. *(275)*
No effect of ozone. Sulfur dioxide was associated with respiratory and cardiovascular deaths.	Zmirou et al. *(276)*
Nitrogen dioxide and ozone were positively related with elderly mortality (RR 1.05 and 1.09, respectively) and cardiovascular mortality (RR 1.07 and 1.09, respectively) during the summer, but not during the winter. Positive associations with black smoke and sulfur dioxide.	Sunyer et al. *(277)*
Single pollutant models disclosed a RR of 1.029 for 200 μg/m^3 1-h ozone. The effect of ozone became non-significant in three pollutant models when the association was dominated by TSP.	Loomis et al. *(278)*
An increase of 40 μg/m^3 ozone was associated with a 2% increment in mortality. Stronger associations were obtained for TSP.	Moolgavkar et al. *(274)*
An increase of 50 μg/m^3 in ozone (1-h maximum) was associated with a 2.9% increase in the daily number of deaths. Positive effects of nitrogen dioxide.	Touloumi et al. *(279)*
An increase of 20 μg/m^3 ozone (1-h maximum) was associated with a 1.6 increase in the daily number of deaths. Positive effects of black smoke.	Simpson et al. *(280)*
RR 1.06 for a change of 67 μg/m^3 ozone. Black smoke also exhibited positive association with mortality.	Hoek et al. *(281)*
An increase in daily 1-h ozone from the 10th to the 90th percentiles was associated with an increase of 2.04% (0.37–3.73) in all-cause mortality and 2.52% (–0.25–5.38) in cardiovascular mortality. Particles and nitrogen dioxide exhibited significant effects.	Morgan et al. *(282)*
A 20 μg/m^3 ozone increase was associated with a 9.9% increase in cardiovascular mortality. PM_{10} had the most robust associations.	Ponka et al. *(283)*
A 50 μg/m^3 increase in 8-h ozone was associated with cardiovascular (RR 1.02) and respiratory (RR 1.06) mortality. Positive results for black smoke and sulfur dioxide.	Zmirou et al. *(284)*
An increase in 100 μg/m^3 for 1-h ozone was associated with a RR 1.015 in Seoul and 1.020 in Ulsan. Positive effects of TSP.	Lee et al. *(285)*
An increase of 20 μg/m^3 ozone was associated with an excess of 3% in mortality. The most consistent associations were obtained for $PM_{2.5}$.	Loomis et al. *(286)*
An increase of 30 μg/m^3 ozone had a RR 1.010 (95% CI 1.002–1.017). Positive effects for the remaining pollutants.	Kwon et al. *(287)*

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Location	End-point	Other pollutants considered
São Paulo	Respiratory mortality in children	PM_{10}, nitrogen dioxide, sulfur dioxide and carbon monoxide
Rouen and Le Havre	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{13}, black smoke, sulfur dioxide and nitrogen dioxide
Montreal	Several causes, including respiratory, cardiovascular, malignancies and diabetes	Sulfur dioxide, nitrogen dioxide, nitric oxide, carbon monoxide, coefficient of haze and predicted PM_{10}
Seven Spanish cities	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{10}, black smoke and nitrogen dioxide
Seoul	Stroke	TSP, sulfur dioxide, nitrogen dioxide and carbon monoxide
Mexico City	All causes (excluding accidents)	PM_{10}
Taipei	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{10}, sulfur dioxide, nitrogen dioxide and carbon monoxide
Helsinki	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{10}, black carbon, TSP, sulfur dioxide, nitrogen dioxide and carbon monoxide
Ninety-five urban communities in the USA	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{10}
Twenty-three European cities	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{10}, sulfur dioxide, nitrogen dioxide and carbon monoxide
Meta-analysis of studies conducted in several European cities	All causes (excluding accidents), respiratory disease and cardiovascular disease	
Fourteen communities in the USA	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{10}
Meta-analysis of 144 effect estimates from 39 time series studies	All causes (excluding accidents), respiratory disease and cardiovascular disease	PM_{10} or $PM_{2.5}$

Observed effect	Reference
No effect of ozone. Positive associations with PM_{10}, sulfur dioxide and carbon monoxide.	Conceicao et al. *(288)*
In Rouen, an interquartile range increase of 60.5–94.1 μg/m^3 of ozone was associated with an increase of 4.1% (95% CI 0.6–7.8) of total mortality. Positive effects of the remaining pollutants.	Zeghnoun et al. *(289)*; Thurston & Ito *(290)*
An increment of 21 μg/m^3 (moving average of 3 days) was associated with the following excesses in mortality: 3.3% (total mortality), 3.9% (cancer), 2.5% (cardiovascular diseases) and 6.6% (respiratory).	Goldberg et al. *(291)*
An increase of 20 μg/m^3 ozone was associated with an increase of 0.56% in cardiovascular mortality. Positive effects of nitrogen dioxide.	Saez et al. *(292)*
An increase of 34 μg/m^3 ozone had a RR 1.06 (95% CI 1.02–1.10) . Positive associations with the remaining pollutants.	Hong et al. *(293)*
An increase of 20 μg/m^3 of ozone was associated with an increment of 0.64% in total mortality. The effect was greater in the elderly group (0.78% for an increase of 20 μg/m^3).	O'Neill et al. *(294)*
No significant associations.	Yang et al. *(295)*
Significant mortality associations between spring and summer ozone levels and respiratory disease (4.30% increase per 10 μg/m^3 of the 4-day mean ozone level) and total (2.42% increase per 10 μg/m^3 of the 4-day mean ozone level).	Penttinen et al. *(296)*
A 20-μg/m^3 increase in ozone was associated with a 0.52% increase in total mortality and 0.64% increase in cardiovascular and respiratory mortality.	Bell et al. *(297)*
No significant effects were observed during the cold half of the year. For the warm season, an increase in 1-h ozone concentration by 10 μg/m^3 was associated with increases of 0.33% (CI 0.17–0.52) in the total daily number of deaths, of 0.45% (95% CI 0.22–0.69) in the number of cardiovascular deaths and of 1.13% (95% CI 0.62–1.48) in the number of respiratory deaths.	Gryparis et al. *(298)*
A 10-μg/m^3 increase in ozone was associated with a RR of 1.003 (1.001–1.004) for all-cause mortality and 1.004 (1.003–1.005) for cardiovascular mortality. The RR for respiratory mortality was 1.000 (0.996–1.005).	Anderson et al. *(299)*
A 20-μg/m^3 increase in hourly ozone was associated with a 0.23% (CI 0.01–0.44) increase in the risk of death.	Schwartz *(300)*
A 10-μg/m^3 increase in ozone was associated with a 0.87% (0.55–1.18) increase in total mortality for all seasons and 1.34% increase (–0.45–3.17) in the warmer season. For cardiovascular disease, the same increment of ozone was associated with a 1.11% (0.68–1.53) increase during all seasons and a 2.45% increase (0.88–4.1) in the warmer season.	Bell et al. *(301)*

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Location	End-point	Other pollutants considered
▶ Meta-analysis of 43 studies conducted in different parts of the world plus an additional analysis in 7 cities in the USA	All causes (excluding accidents), PM_{10} or $PM_{2.5}$	
Meta-analysis of 28 studies	All causes (excluding accidents), PM_{10} or $PM_{2.5}$	PM_{10}, $PM_{2.5}$, sulfur dioxide, nitrogen dioxide and carbon monoxide

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Observed effect	Reference
A 0.39% increase (95% CI 0.26–0.51) in mortality per 20-μg/m^3 increase in 1-h daily maximum ozone. No appreciable modification by including PM as co-pollutant in the models. Effects were larger for the warmer season.	Ito et al. *(302)*
A 0.21% increase (CI 0.16–0.26) in mortality per 10-μg/m^3 increase in 1-h maximum ozone.	Levy et al. *(303)*

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Annex 2

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The WHO air quality guidelines offer guidance on reducing the effects on health of air pollution. This book presents revised guideline values for the four most common air pollutants – particulate matter, ozone, nitrogen dioxide and sulfur dioxide – based on a recent review of the accumulated scientific evidence. The rationale for selection of the guideline value is supported by a synthesis of information emerging from research on the health effects of each pollutant.

The book gives a brief yet comprehensive review of the issues affecting the application of the guidelines in risk assessment and policy development. It summarizes information on pollution sources and levels in various parts of the world, on population exposure and characteristics affecting sensitivity to pollution, on methods for quantifying the health burden of air pollution, and on the use of guidelines in developing air quality standards and other policy tools. The special case of indoor air pollution is also explored.

Prepared by a large team of renowned international experts who considered conditions in various parts of the globe, these guidelines are applicable throughout the world. They provide reliable guidance for policy-makers everywhere when considering the various options for air quality management.

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ISBN 92 890 2192 6